STUDIES ON MODIFIED STEROIDS

RESUME

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

TO

THE ALIGARH MUSLIM UNIVERSITY,
ALIGARH

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DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH

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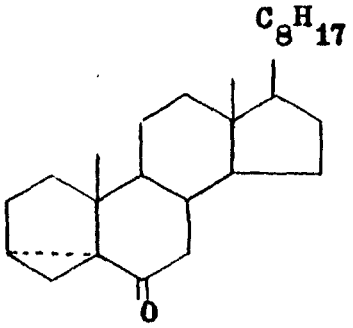
R E S U M E

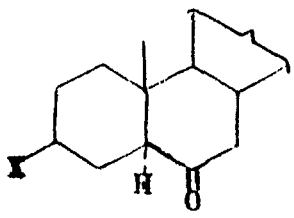
PART-I

Baeyer-Villiger oxidation of steroidal ketones

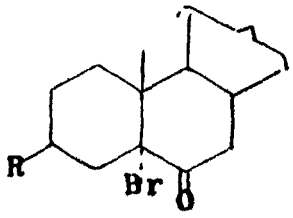
The Baeyer-Villiger oxidation of steroidal ketones, both saturated as well as α,β-unsaturated ones, has been extensively studied. In the preceding years, a number of communications from our laboratories described the work on the synthesis of oxasteroids. The substrates on which previous studies centred were 3α-5-cyclo-5α-cholestan-6-one (I), its 3β-haloderivatives (II-IV), 5-bromo-5α-cholestan-6-one (V), its 3β-acetoxy analogue (VI), cholest-4-en-6-one (VII), its 3β-acetoxy analogue (VIII), cholest-4-ene,3,6-dione (IX) and 3β-acetoxystigmast-4-en-6-one (X).



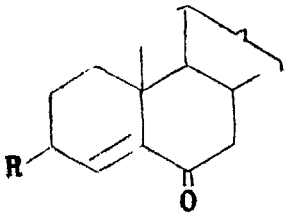
(I)



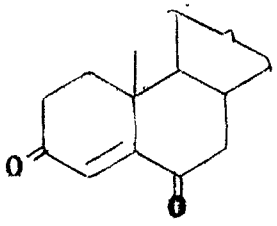
(II) X, Cl
(III) X, Br
(IV) X, I



(V) R, H
(VI) R, OAc



(VII) R, H
(VIII) R, OAc



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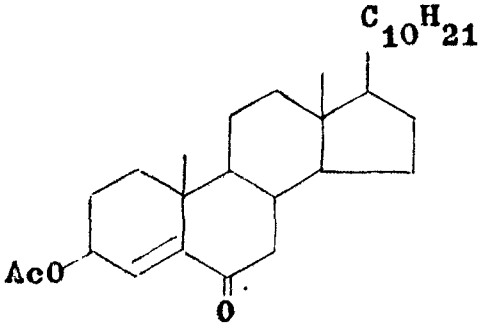
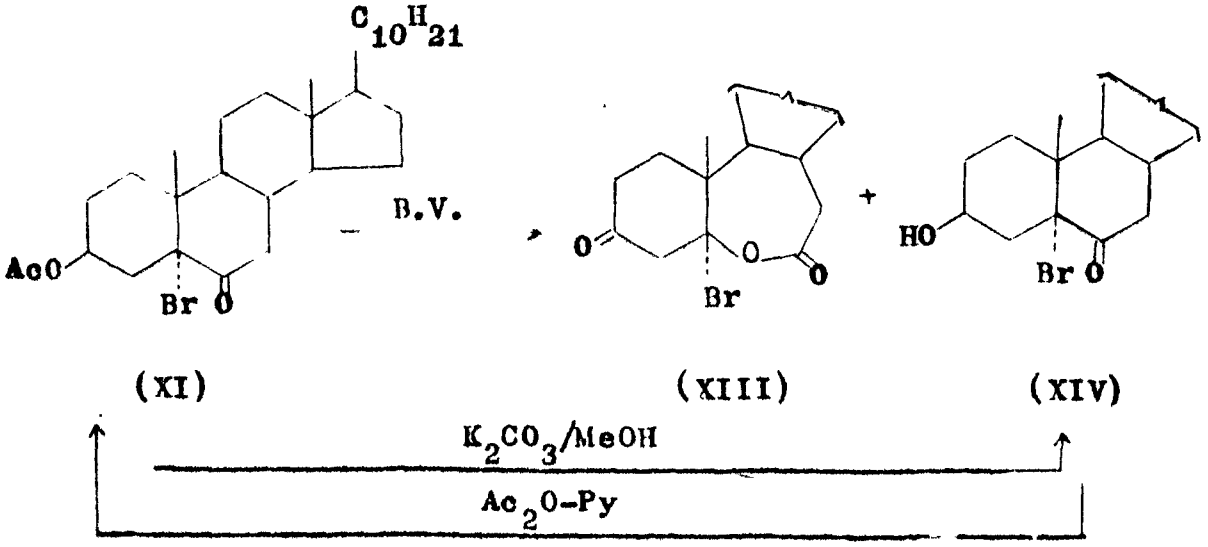
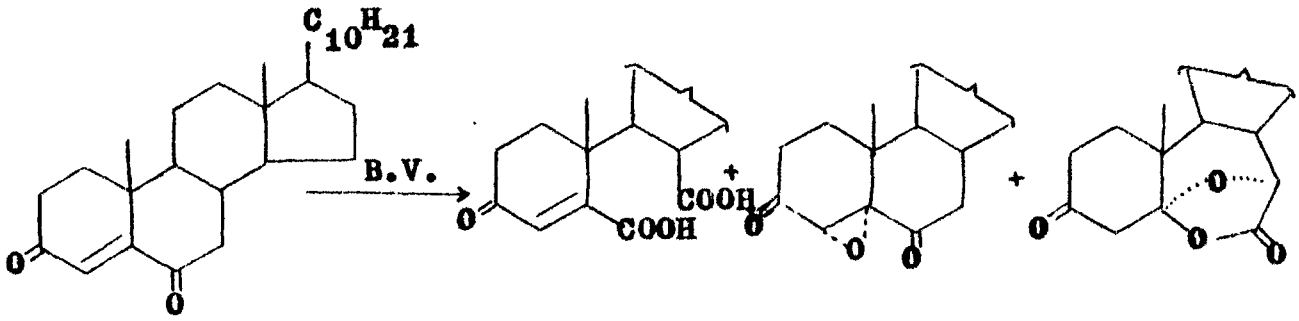


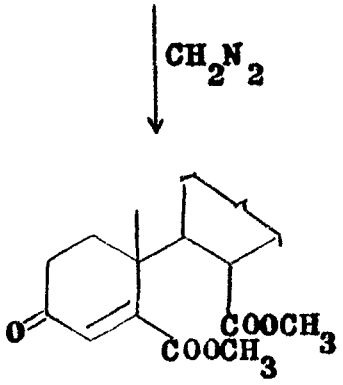
(X)

The present work is concerned with the Baeyer-Villiger oxidation of steroidal ketones in the stigmastane series. The substrates subjected to this reaction are 3β-acetoxy-5α-bromostigmastan-6-one (XI) and stigmast-4-ene-3,6-dione (XII). The products obtained have been characterized on the basis of their spectral and chemical properties. The results are summarized in the following flow sheet.





(XII) (XV) (XVI) (XVII)



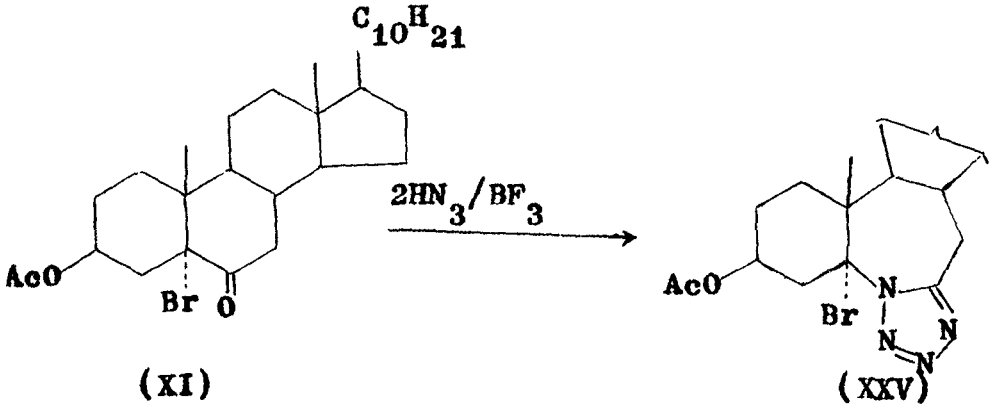
(XVIII)

PART-II

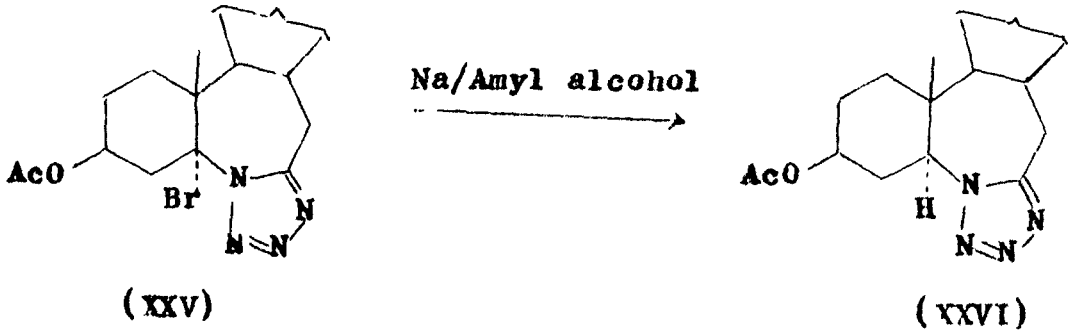
Steroidal Tetrazoles

Steroidal tetrazoles in the preceding years have gained vital significance because of their biological activity. Recently, several papers appeared describing the synthesis of steroidal tetrazoles mainly in the cholestane series. We have made attempts to prepare saturated as well as unsaturated tetrazoles belonging to the stigmastane series. The substrates

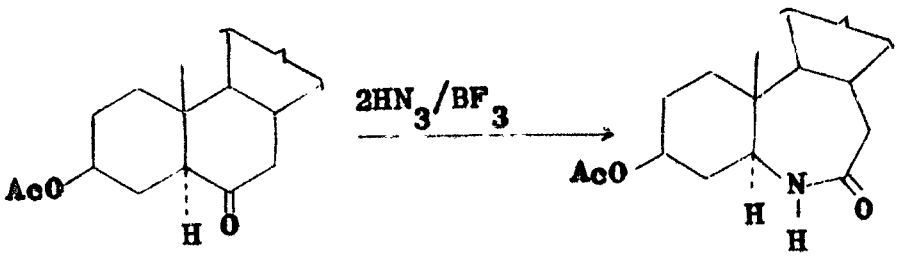
employed for the reaction are 3β-acetoxy-5α-bromostigmastan-6-one (XI), 3β-acetoxy-5α-stigmastan-6-one (XIX), 5α-stigmastane-3,6-dione (XX), stigmast-5-en-7-one (XXI), its 3β-acetoxy (XXII), 3β-chloro (XXIII) and 3β-hydroxy (XXIV) analogues. The products obtained have been characterized on the basis of their spectral data and chemical transformations. The outcome of the study is embodied in the flow sheets given below.



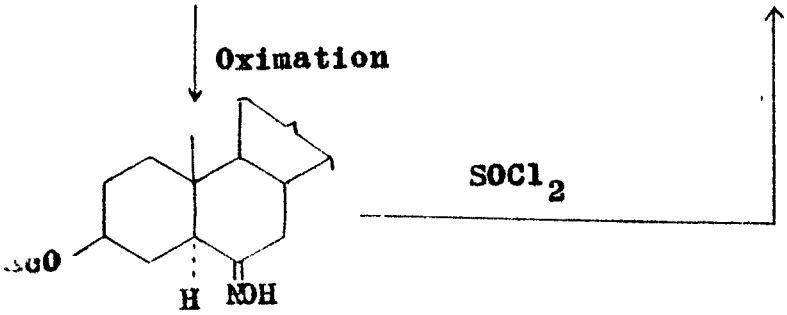
(XI) (XXV)



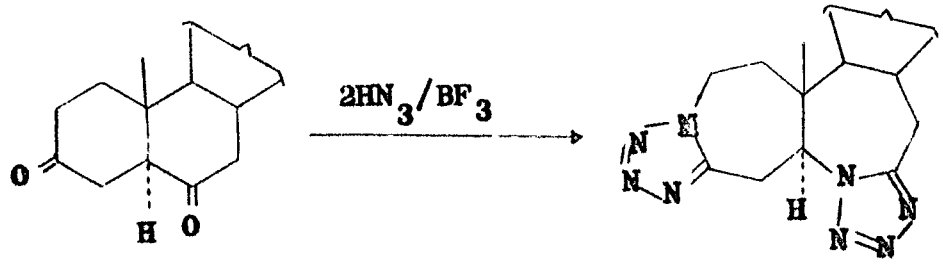
(XXV) (XXVI)



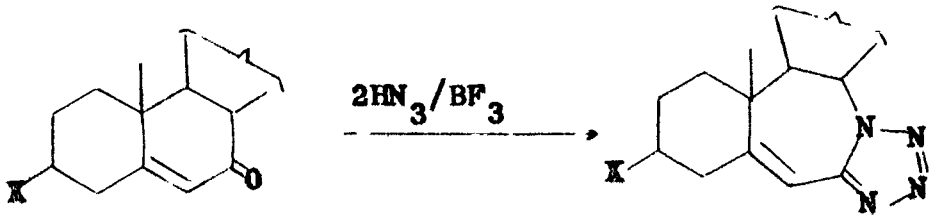
(XIX) (XXVI) (XXVII)



(XXVIII)



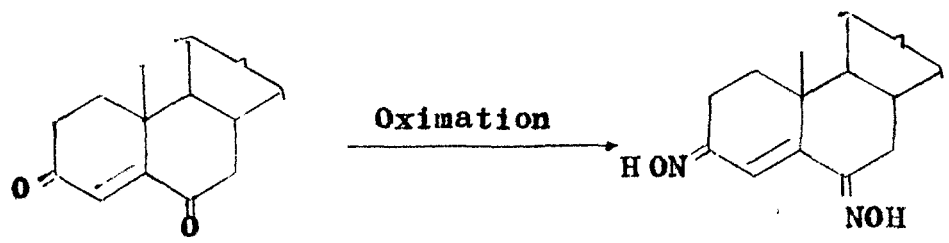
(XX) (XXIX)



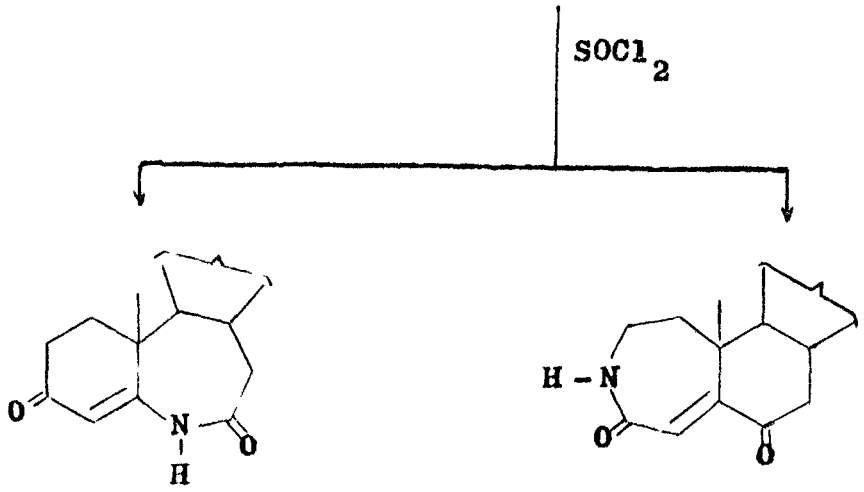
(XXI) X, H
(XXII) X, OAc
(XXIII) X, Cl
(XXIV) X, OH

(XXX) X, H
(XXXI) X, OAc
(XXXII) X, Cl
(XXXIII) X, OH

The diketone (XII) was also subjected to oximation and subsequently the dioxime (XXXIV) obtained was allowed to react with $SOCl_2$, under the conditions of Beckmann rearrangement. It yielded the monolactams (XXXV) and (XXXVI). Those monolactams were characterized on the basis of their spectral evidences and elemental analysis.



(XII) (XXXIV)

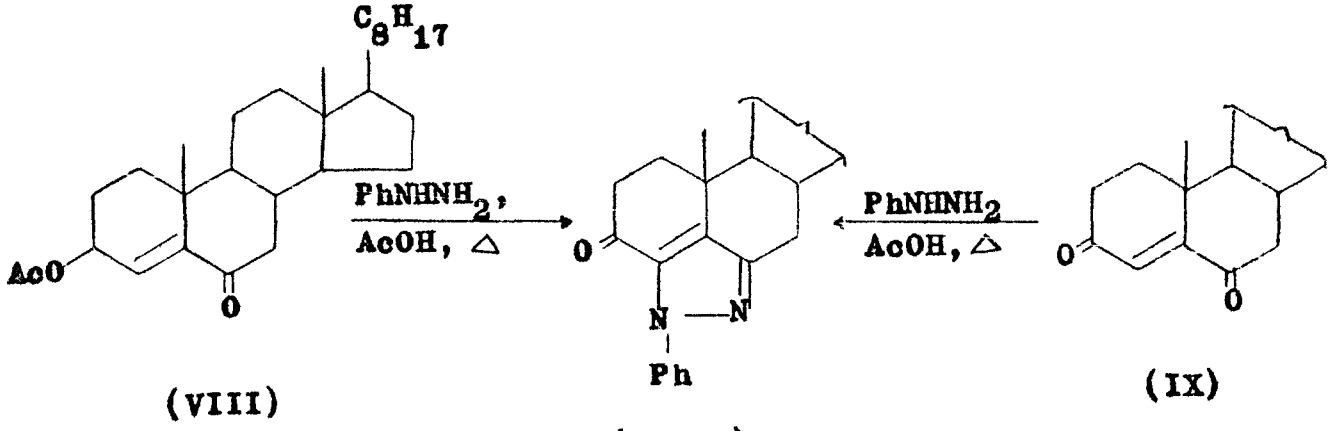


(XXXV) (XXXVI)

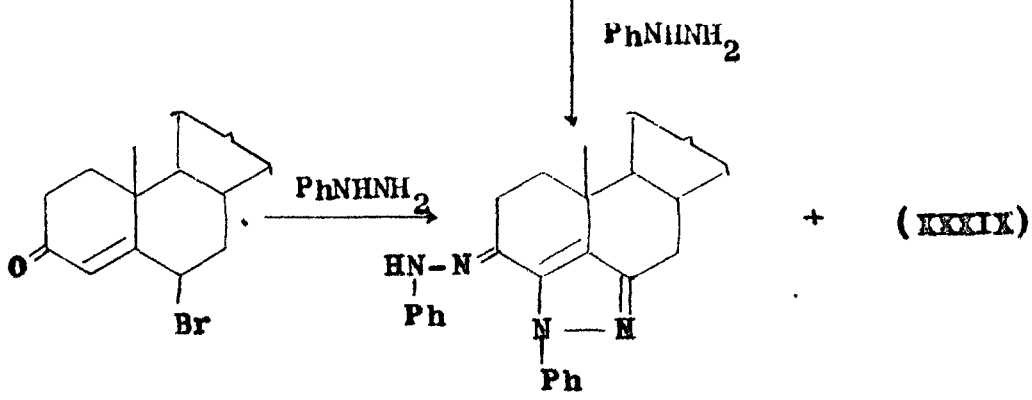
PART-III

Steroidal Pyrazoles

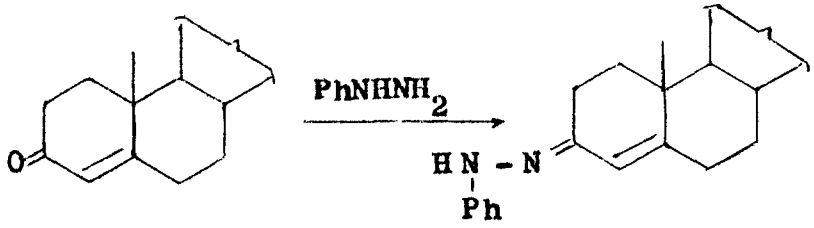
In the recent past, the synthesis of steroidal pyrazole derivatives has attracted the attention of organic chemists because of the unusual physiological activity and profound endocrinological interests associated with them. With this realization, some papers appeared dealing with the synthesis of pyrazolosteroids from various α,β-unsaturated steroidal ketones mainly in the androstane series. It was noted that little attention has been paid towards the synthesis of such compounds in the cholestane series. This prompted us to undertake the work in this area. We subjected some of the easily accessible α,β-unsaturated ketones such as 3β-acetoxycholest-4-en-6-one (VIII), cholest-4-ene-3,6-dione (XIX), 6β-bromocholest-4-en-3-one (XXXVII) and cholest-4-en-3-one (XXXVIII) to the reaction with phenyl hydrazine. The products obtained have been characterized on the basis of spectral behaviour, chemical transformations, mechanistic studies and general considerations. However, the work at this stage is primarily of exploratory nature. The results are summarized in the flow sheet given below.



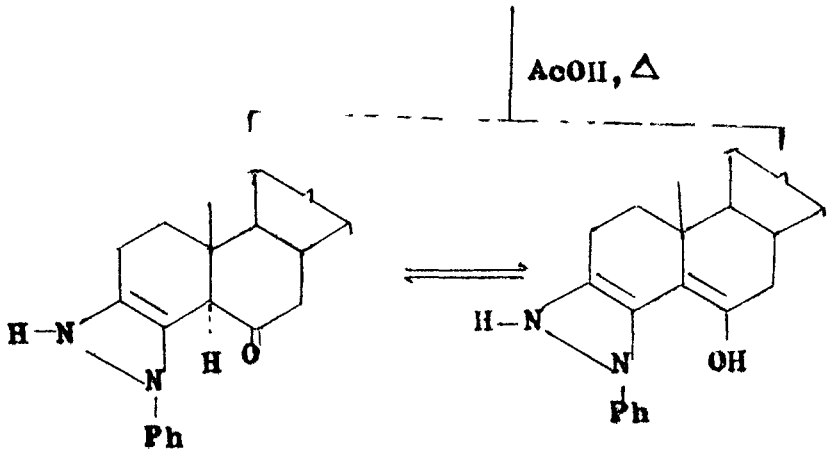
(VIII) (XXXIX) (IX)



(XXXVII) (XL) (XXXIX)



(XXXVIII) (XLI)



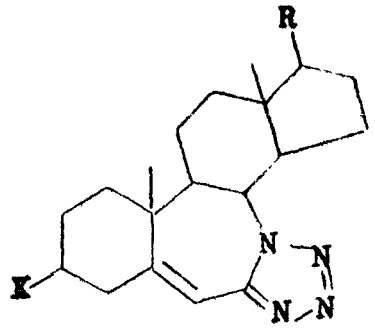
(XLII) (XLIII)

Interestingly, the reaction of the ketones (VIII) and (XIX) under similar conditions yielded the same pyrazole (XXXIX) while the bromoketone (XXXVII) gave the compound (XL) in addition to the pyrazole (XXXIX). Attempts have been made to rationalize these observations. Further, the ketone (XXXVIII) reacted differently under similar reaction condition which yielded the products (XLI-XLIII).

PART-IV

Mass Spectrometry of Steroidal Tetrazoles

Recently, a number of communications on the synthesis of steroidal tetrazoles have appeared from our laboratories. The present study is concerned with the mass spectrometry of some 7a-azatetrazoles in the stigmastane and the cholestane series. The compounds studied are 7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (XXX), 3β-acetoxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (XXXI), 3β-chloro-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (XXXII) and 3β-hydroxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (XXXIII) along with their 3β-substituted analogues (XLIV-XLVI), in the cholestane series.



	X	R
(XXX)	H	$C_{10}H_{21}$
(XXXI)	OAc	$C_{10}H_{21}$
(XXXII)	Cl	$C_{10}H_{21}$
(XXXIII)	OH	$C_{10}H_{21}$
(XLIV)	OAc	C_8H_{17}
(XLV)	Cl	C_8H_{17}
(XLVI)	OH	C_8H_{17}

All the spectra of 3β-substituted 7a-azatetrazoles are conspicuous by the presence of a common fragment ion peak at m/z 175 and the corresponding peak at m/z 177 was observed in the case of (XXX), which may be considered to be of diagnostic value in the characterization of such structurally related compounds. Structural similarities in these tetrazoles gave hope of similar fragmentation pathways. However, all the expectations were not fully realized as the substituents at C_3 influenced the fragmentation in no uncertain terms. Fragmentation pathways have been suggested and an attempt has been made to stablish structure-spectra relationship.

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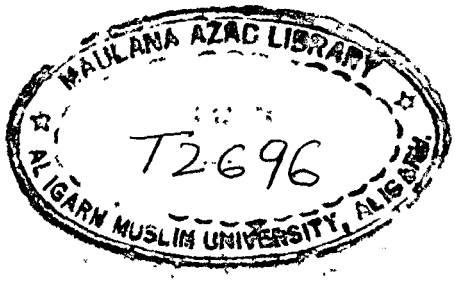

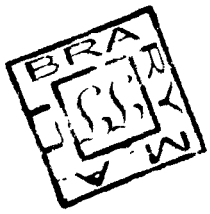

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This is to certify that the work described in the thesis is the original work of the candidate accomplished under my supervision. The thesis is suitable for submission for the award of Ph.D. degree in Chemistry.

M. S. Ahmad

(M. SHAHABUDDIN AHMAD)
Professor of Chemistry

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The author wishes to express his gratitutde to Professor M. Shahabuddin Ahmad, who directed these researches, for his unstinted help, guidance and encouragement and to Professor W. Rahman, Chairman, Department of Chemistry for providing necessary facilities.

Thanks are also due to my research colleagues for their help and sincere suggestions. Financial assistance from CSIR, New Delhi is gratefully acknowledged.

(SHAMIM AHMAD ANSARI)

D E D I C A T E D

To

M Y P A R E N T S

C O N T E N T S

THEORETICAL

Oxasteroids

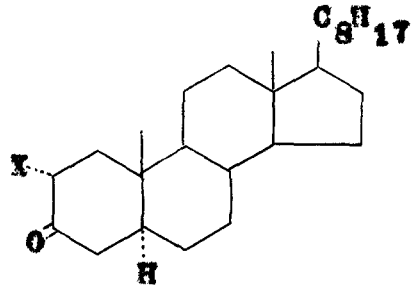
Oxasteroids, steroidal compounds containing oxygen as a part of the nucleus, have been extensively prepared by a variety of methods for their many fold biological activities and their importance as intermediates in many reactions. As intermediates, they became important for the insertion of labelled oxygen into the steroid nucleus, ring contraction, preparation of methyl derivatives etc. Oxasteroids are usually prepared in the form of an ether, lactone, anhydride and as derivatives of lactones by various methods. These include (i) via keto acids, (ii) direct formation of cyclic products, (iii) from azasteroids, (iv) via seco-dihydroxy compounds, (v) lactone reduction, (vi) via seco acid aldehydes, (vii) microbiological methods, (viii) X-ray radiation and other miscellaneous methods. A review on the literature on insertion of hetero atoms in steroid nucleus has been given by Tokes.[1]

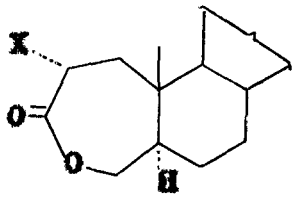
Baeyer and Villiger[2] reported the first example of the peracid oxidation of ketones to esters or lactones in 1899. Since that time this type of oxidation has found a wide variety of important synthetic and degradative applications. Peracids have been used to synthesize a variety of steroid and terpene

lactones as well as lactones involving medium and large size rings which are virtually unobtainable by other means. A thorough review on the subject is given by Hassall.[3]

Baeyer-Villiger oxidation of steroidal ketones

Bolliger and Courtney[4] carried out the oxidation of 2α-halo-5α-cholestan-3-ones (I) and (II) with trifluoroperoxy-acetic acid in chloroform and obtained 2α-halo-4-oxa-A-homo-5α-cholestan-3-ones (III) and (IV), respectively. The non-formation of 3-oxa isomeric lactones suggested that the presence of an α-halogen at C_2-position apparently has curtailed the migratory aptitude of C_2 in comparison to C_4.



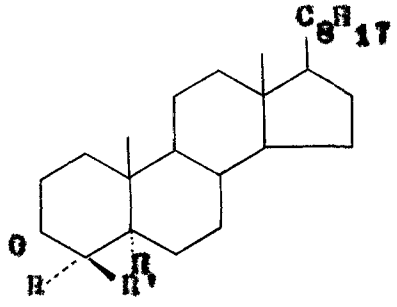


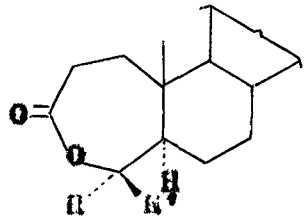
(I) X, Cl
(II) X, Br

(III) X, Cl
(IV) X, Br

The Baeyer-Villiger oxidation of 4α- and 4β-methyl-5α-cholestan-3-ones (V) and (VI) and 4,4-dimethyl-5α-cholestan-3-one (VII) with m-chloroperbenzoic acid afforded the ∈ -lactones,

4aα-methyl-4-oxa-A-homo-5α-cholestan-3-one (VIII), 4aβ-methyl-4-oxa-A-homo-5α-cholestan-3-one (IX) and 4a,4a-dimethyl-4-oxa-A-homo-5α-cholestan-3-one (X), respectively, showing thereby that a more substituted carbon migrates preferentially.[5] Interestingly, oxidation of the ketone (VII) in the presence of a mineral acid as the catalyst gave the lactone (VIII) with the loss of a methyl group.[6]

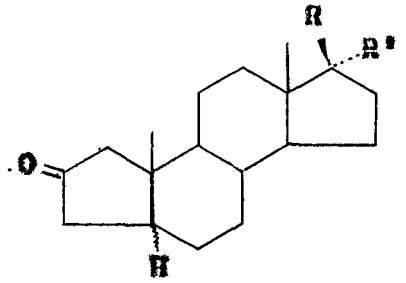




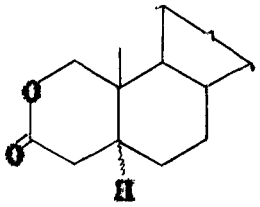
(V) R, Me; R', H
(VI) R, H; R', Me
(VII) R, Me; R', Me

(VIII) R, Me; R', H
(IX) R, H; R', Me
(X) R, Me; R', Me

Nara[7] has shown that the Baeyer-Villiger oxidation of some 5α- and 5β-2-keto-A-nor steroids (XI) gave exclusively 2-oxasteroids (XII).



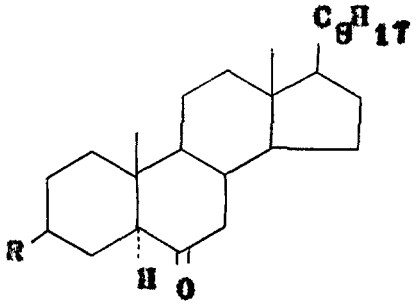
(XI)



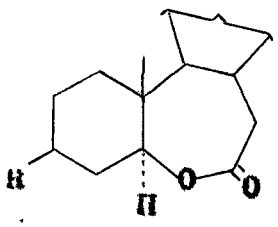
(XII)

a. R, C_8H_{17}; R', H
b. R, H ; R', H
c. R, OH; R', H
d. R, OAc; R', H
e. R, OH; R', CH_3

Ponken and Wiles[9] reported the formation of the lactones (XV) and (XVI) from the Baeyer-Villiger oxidation of 5α-cholestan-6-one (XIII) and 3β-acetoxy-5α-cholestan-6-one (XIV), respectively.

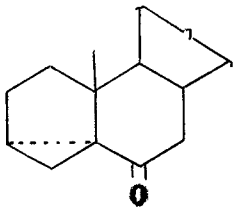


(XIII) R, H
(XIV) R, OAc

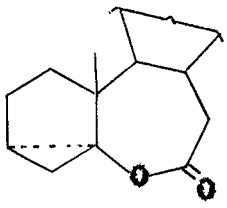


(XV) R, H
(XVI) R, OAc

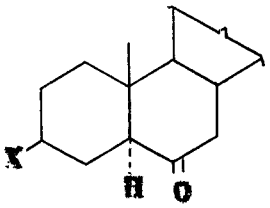
Ahmad et al.[9] have reported the Baeyer-Villiger oxidation of 3α,5-cyclo-5α-cholestan-6-one (XVII) and its 3β-halo derivatives (XVIII), (XIX) and (XX). They obtained the corresponding 6-oxa compounds, (XXI), (XXII), (XIII) and (XIV), respectively.



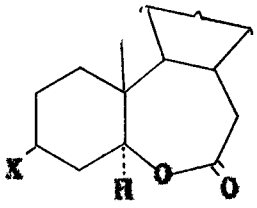
(XVII)



(XXI)

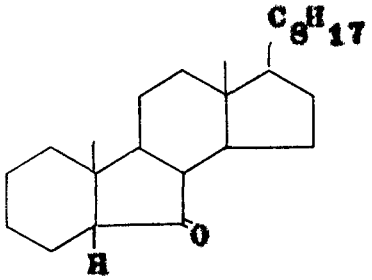


(XVIII) X, Cl
(XIX) X, Br
(XX) X, I

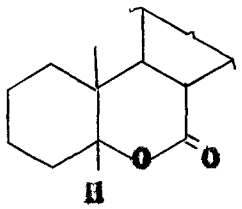


(XXII) X, Cl
(XXIII) X, Br
(XXIV) X, I

The Baeyer-Villiger oxidation of B-nor-5β-cholestan-7-one (XXV) with trifluoroperacetic acid afforded 6-oxa-3β-cholestan-7-one (XXVI).[10]

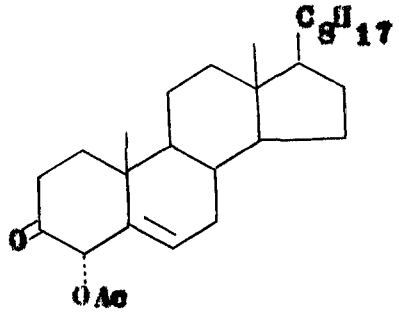


(XXV)

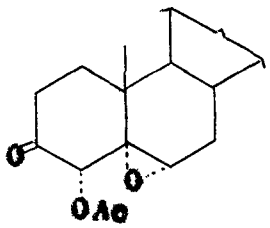


(XXVI)

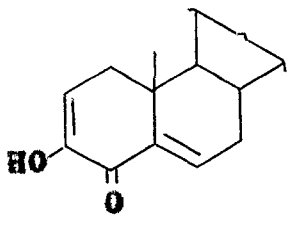
Recently Ahmad et al.[11] reported the Baeyer-Villiger oxidation of 4α-acetoxy-cholest-5-en-3-one (XXVII) with different concentrations of perbenzoic acid monohydrate as catalyst. The ketone (XXVII) with one mole equivalent of perbenzoic acid gave 5,6-epoxy-4α-acetoxy-5α-cholestan-3-one (XXVIII), 3-hydroxy-cholesta-2,5-dien-4-one (XXIX) and 6β-hydroxy-4-acetoxycholest-4-en-3-one (XXX). The same ketone (XXVII) with 2.5 mole equivalent of perbenzoic acid afforded only 5,6β-dihydroxy-4aα-acetoxy-4-oxa-A-homo-5α-cholestan-3-one (XXXI).



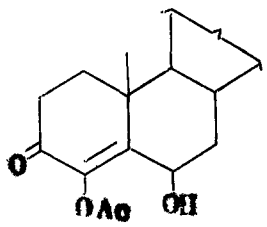
(XXVII)



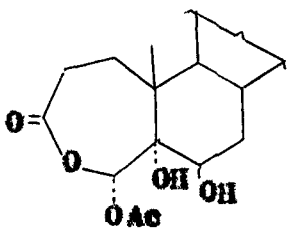
(XXVIII)



(XXIX)

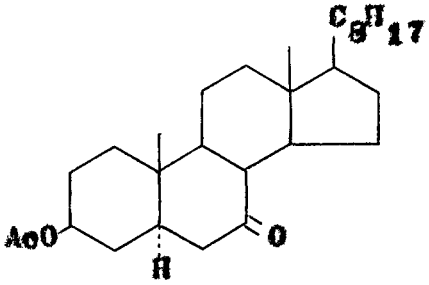


(XXX)

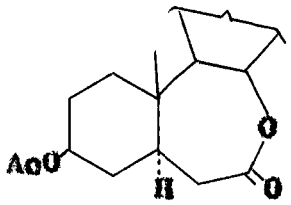


(XXXI)

Plattner et al.[12] reported that 3β-acetoxy-5α-cholestan-7-one (XXXII) under the Baeyer-Villiger oxidation conditions afforded a single lactone, 3β-acetoxy-7a-oxa-8-homo-5α-cholestan-7-one (XXXIII).

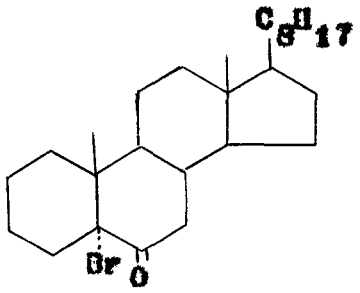


(XXXII)

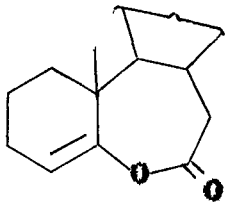


(XXXIII)

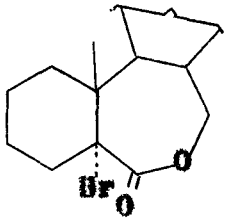
Ahmad and Parooq[13] reported the Baeyer-Villiger oxidation of α-bromo-steroidal ketones to investigate the effect of substituents in the close vicinity of ketonic function on the course of the reaction. The perbenzoic acid oxidation of 5α-bromocholestan-6-one (XXXIV) and 3β-acetoxy-5α-bromocholestan-6-one (XXXV), after one week, yielded 7a-bromo-6-oxa-8-homocholest-4-en-7-one (XXXVI), 6-oxa-8-homo-5α-bromocholestan-7-one (XXXVII) and 7-oxa-8-homo-5α-bromocholestan-6-one (XXXVIII). However, the ketone (XXXV) after 24 hours, afforded 3β-hydroxy-4α-5-epoxy-7-oxa-8-homo-5α-cholestan-6-one (XXXIX), 3β-hydroxy-5α-bromo-7-oxa-8-homocholestan-6-one (XL) and 3β-benzoyloxy-4α-5-epoxy-7-oxa-8-homo-5α-cholestan-6-one (XLI).



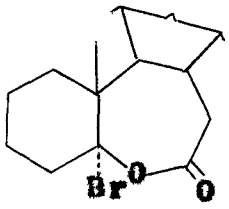
(XXXIV)



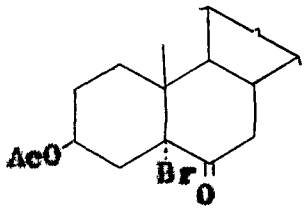
(XXXVI)



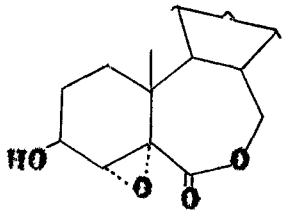
(XXXVIII)



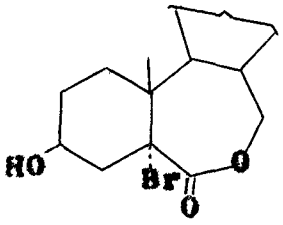
(XXXVII)



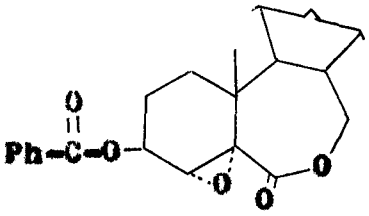
(XXXV)



(XXXIX)



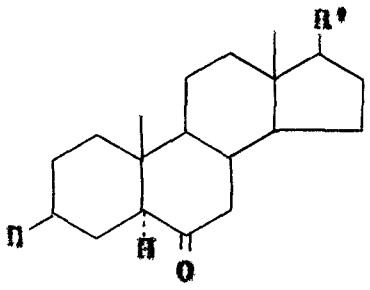
(XL)



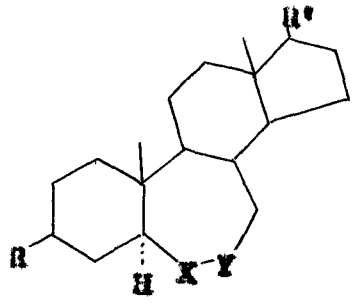
(XLI)

The Baeyer-Villiger oxidation[14] of 3β-acetoxy-5α-stigmastan-6-one (XLII) gave two isomeric lactones, 3β-acetoxy-6-oxa-7-homo-5α-stigmastan-7-one (XLIII) and 3β-acetoxy-7-oxa-8-homo-5α-stigmastan-6-one (XLIV). This led to reinvestigation

of the Baeyer-Villiger oxidation of other 6-ketones in the cholestane series such as (XIII), (XIV), (XVIII) and (XIX) and in all these cases isomeric lactones were obtained. This observation was further substantiated by ^{13}C NMR spectral studies.[14a]



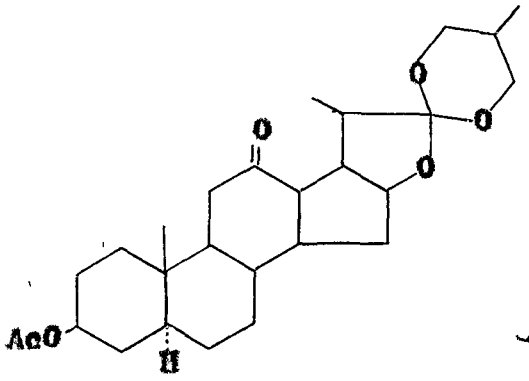
	R	R'
(XIII)	H	C_8H_{17}
(XIV)	OAc	C_8H_{17}
(XVIII)	Cl	C_8H_{17}
(XIX)	Br	C_8H_{17}
(XLII)	OAc	$C_{10}H_{21}$



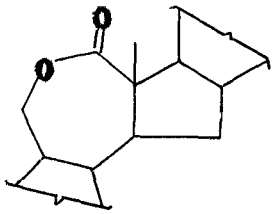
	R	R'	X	Y
(XV)	H	C_8H_{17}	O	C=O
(XLV)	H	C_8H_{17}	C=O	O
(XVI)	OAc	C_8H_{17}	O	C=O
(XLVI)	OAc	C_8H_{17}	C=O	O
(XXII)	Cl	C_8H_{17}	O	C=O
(XLVII)	Cl	C_8H_{17}	C=O	O
(XXIII)	Br	C_8H_{17}	O	C=O
(XLVIII)	Br	C_8H_{17}	C=O	O
(XLIII)	OAc	$C_{10}H_{21}$	O	C=O
(XLIV)	OAc	$C_{10}H_{21}$	C=O	O

The Baeyer-Villiger oxidation of hecogenin acetate (XLV) with peracetic acid and perbenzoic acid in presence of sulphuric acid as the catalyst furnished (XLVI).[15] The ketone (XLV) was

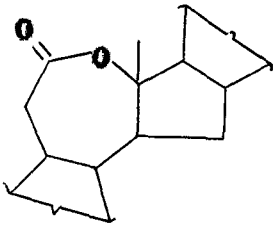
further subjected to the Baeyer-Villiger oxidation under the same conditions by Bladon and McMeekin[16] and they obtained a mixture of the lactones (XLVI) and (XLVII).



(XLV)

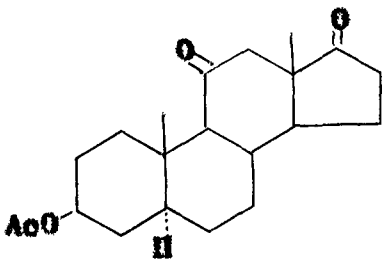


(XLVI)

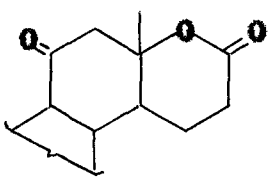


(XLVII)

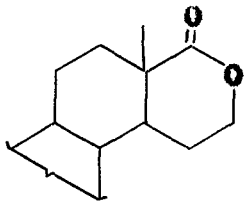
3β-Acetoxy-5α-androstane-11,17-dione (XLVIII) furnished, on oxidation, an isomeric mixture of ring D lactones (XLIX)[17] and (L).[18]



(XLVIII)

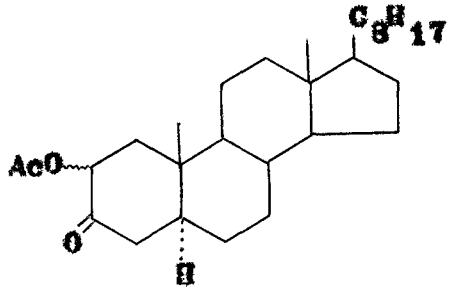


(XLIX)

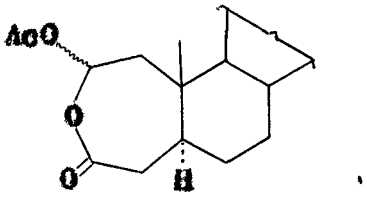


(L)

Baeyer-Villiger oxidation of 2-acetoxy-5α-cholestan-3-ones (CXXXII) and (CXXXIII) afforded the lactones, 2-acetoxy-3-oxa-3-homo-5α-cholestan-4-ones (CXXXIV) and (CXXXV).[19]

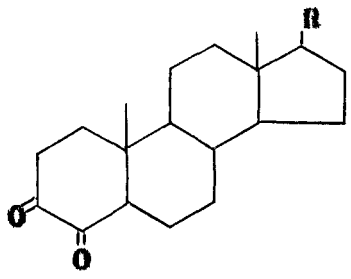


(CXXXII) α -OAc
(CXXXIII) β -OAc

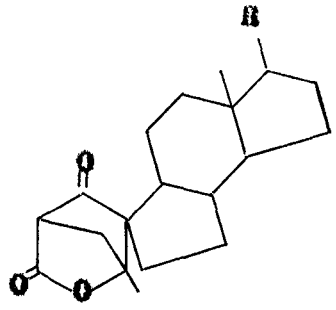


(CXXXIV) α -OAc
(CXXXV) β -OAc

Moiono et al.[20] have reported the oxidation of 3,4-diketosteroids. Treatment of cholestane-3,4-dione (CXXXVI) and 17β-acetoxyandrostane-3,4-dione (CXXXVII) with thallium triacetate in acetic acid provided spiro-lactones (CXXXVIII) and (CXXXIX).



(CXXXVI) R, C_8H_{17}
(CXXXVII) R, OAc

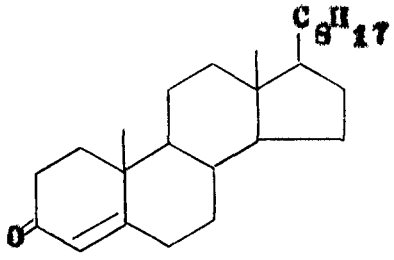


(CXXXVIII) R, C_8H_{17}
(CXXXIX) R, OAc

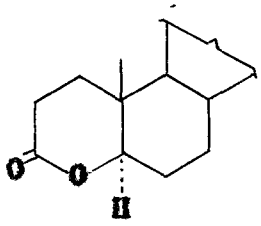
Baeyer-Villiger oxidation of α,β-unsaturated ketones

Peracid oxidation of α,β-unsaturated steroidal ketones may result in the formation of enol esters, epoxylactones and epoxy ketones.[20-24] However, the peracid oxidation of Δ^4-3-ketosteroids may lead to even large variety of products depending on the reaction conditions and the peracid used.

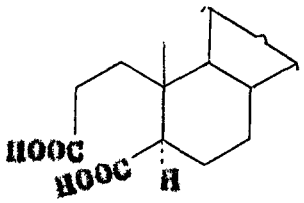
Turner[25] reported the oxidation of cholest-4-en-3-one (LI) with potassium persulphate and sulphuric acid which gave 4-oxa-3α-cholestan-3-one (LII) and dihydro Diels acid (LIII). Petit and Kasturi[26] obtained the lactone (LII) as the sole product on oxidation with peroxysulphuric acid.



(LI)

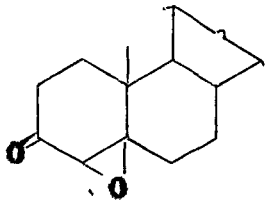


(LII)

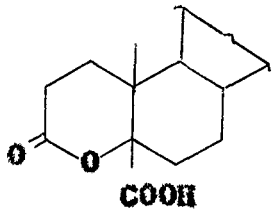


(LIII)

The ketone (LI) when oxidised[27] with alkaline hydrogen peroxide (30%) afforded 4β-epoxy-5β-cholestan-3-one (LIV) which on refluxing with the same reagent gave 4-oxa-5β-cholestan-3-one-5-carboxylic acid (LV).



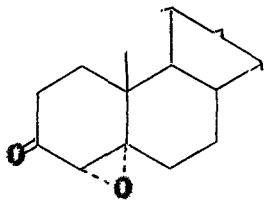
(LIV)



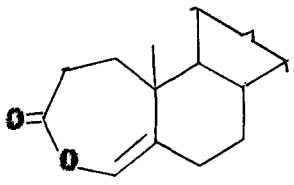
(LV)

The repeated oxidation[28] of (LI) with perbenzoic acid and anhydrous perchloric acid as the catalyst gave 4α,5-epoxy-5α-cholestan-3-one (LVI), 4-oxa-A-homocholest-4a-en-3-one (LVII), 5-formyl-4-oxa-3α-cholestan-3-one (LVIII) and 3,5-seco-4-norcholestan-5-one-2-carboxylic acid (LIX).

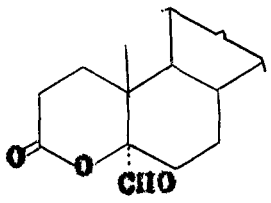
(LI) $\xrightarrow[\text{Perchloric acid}]{\text{PBA}}$



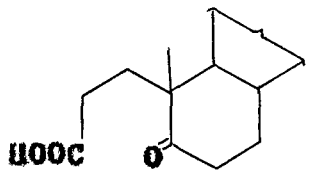
(LVI)



(LVII)

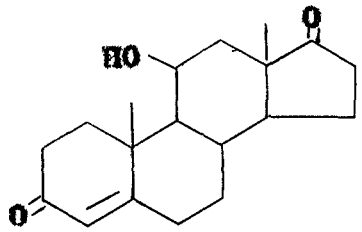


(LVIII)

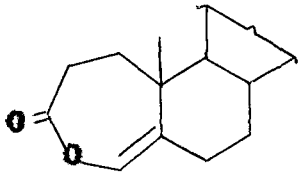


(LIX)

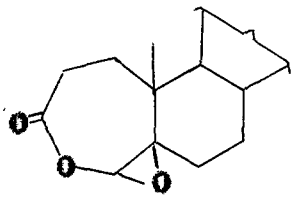
Capsi et al.[29] reported the oxidation of 11β-hydroxy-androst-4-ene-3,17-dione (LX) which yielded the enol lactone, 11β-hydroxy-4-oxa-A-homoandrost-4a-ene-3,17-dione (LXI) and a small quantity of the epoxylactone, 11β-hydroxy-4-oxa-4aβ-5-epoxy-A-homo-5β-androstane-3,17-dione (LXII).



(LX)

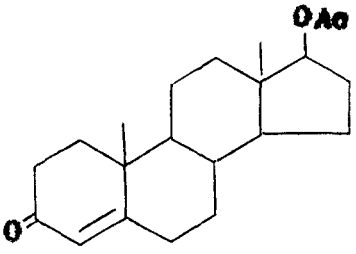


(LXI)

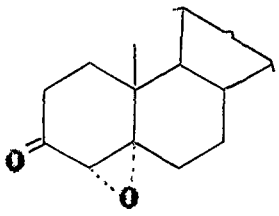


(LXII)

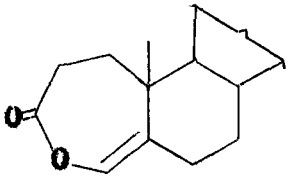
Mazur et al.[30] carried out the oxidation of testosterone acetate (LXIII) with perbenzoic acid (1 mole) in the presence of anhydrous perchloric acid as the catalyst for 12 hrs. and it gave 17β-acetoxy-4α,5α-epoxyandrostan-3-one (LXIV) and 17β-acetoxy-4-oxa-A-homoandrost-4a-en-3-one (LXV).



(LXIII)



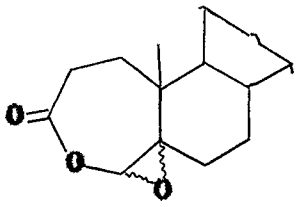
(LXIV)



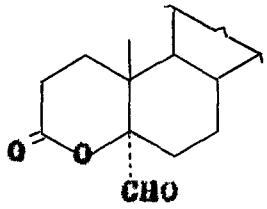
(LXV)

When (LXIII) was further treated with 2 mole equivalent of the peracid for 12 hours, the major products obtained were the epoxylactones, 17β-acetoxy-4α-5-epoxy-4-oxa-A-homoandrostan-3-one (LXVI-a) and (LXVI-b) along with 17β-acetoxy-5-formyl-4-oxa-5α-androstan-3-one (LXVII), 17β-acetoxy-5-formyl-4-oxa-5β-androstan-3-one (LXVIII), the epoxy ketone (LXIV) and methyl 17β-acetoxy-3,5-seco-4-nor-5β-hydroxy-5α-formyl androstan-3-oate (LXIX).

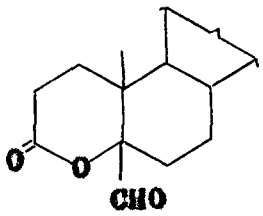
(LXIII) $\xrightarrow[(2\ \text{mole})]{\text{PBA}}$



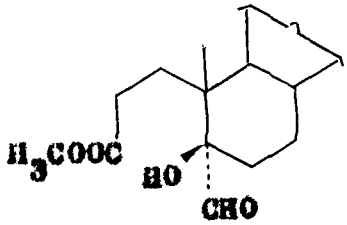
(LXVI-a) 4α,5α
(LXVI-b) 4β,5β



(LXVII)



(LXVIII)



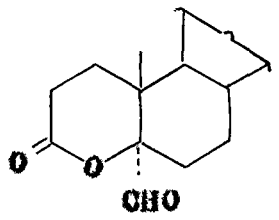
(LXIX)

Extended reaction period increased the yield of the aldehyde lactones (LXVII) and (LXVIII) and decreased the yield of the epoxylactone (LXVI). With these observations, they

assumed that (LXVI-a) and (LXVI-b) are the precursors of (LXVII) and (LXVIII), respectively.

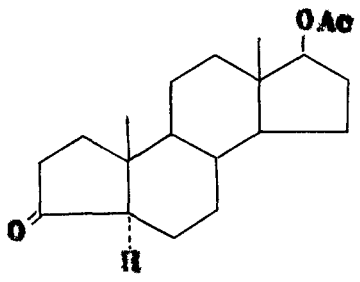
The formation of various products prompted Mazur et al. to extend the reaction period and concentration of perbenzoic acid for further study and they carried out the oxidation of (LXIII) with 4 mole equivalent of perbenzoic acid and perchloric acid as the catalyst for 84 hours which afforded (LXVI-a), (LXVI-b), (LXVII), (LXVIII), (LXIX) and 17β-acetoxy-3-formate-4-oxa-5α-androstan-3-one (LXX).

(LXIII) $\xrightarrow[(4\ \text{mole})]{\text{PBA}}$ (LXVI-a) + (LXVI-b) + (LXVII) + (LXVIII) + (LXIX) +

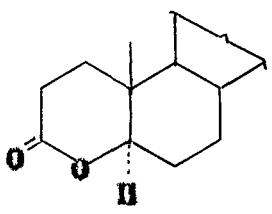


(LXX)

When the reaction was performed with 2 mole equivalent of perbenzoic acid in the presence of aqueous perchloric acid for 12 hours, 17β-acetoxy-A-norandrostan-3-one (LXXI) and the δ-lactone (LXXII) were obtained from (LXIII).

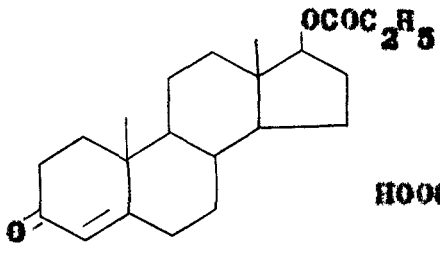


(LXXI)

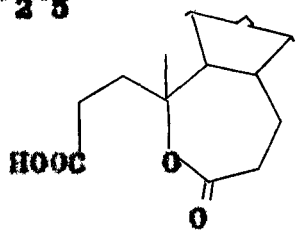


(LXXII)

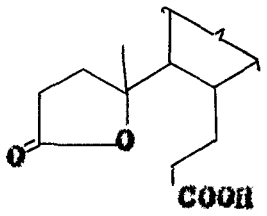
The oxidation of testosterone propionate (LXXIII) was performed with hydrogen peroxide in the presence of selenium dioxide by Caspi and Balasubramanyam[31] and they obtained ϵ-lactone carboxylic acid (LXXIV) and the γ-lactone acid (LXXV).



(LXXIII)

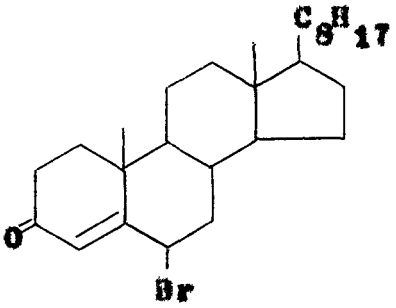


(LXXIV)

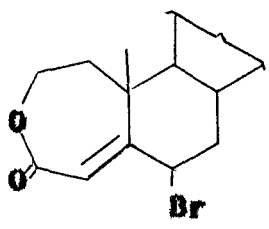


(LXXV)

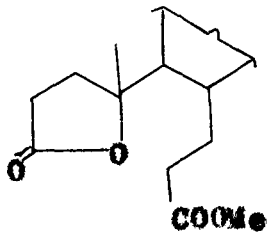
In order to investigate the effect of substituent in the close vicinity of 4-en-3-one moiety on the course of reaction and product distribution, 6β-bromocholest-4-en-3-one (LXXVI) was subjected to perbenzoic acid oxidation which provided the lactone, 6β-bromo-3-oxa-A-homocholest-4a-en-4-one (LXXVII) a product of primary oxidation and a bromine free γ-lactone methyl ester (LXXVIII).[32] However, the enol lactone (LXXIX) was not obtained.



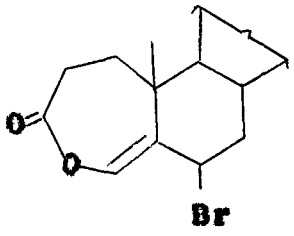
(LXXVI)



(LXXVII)



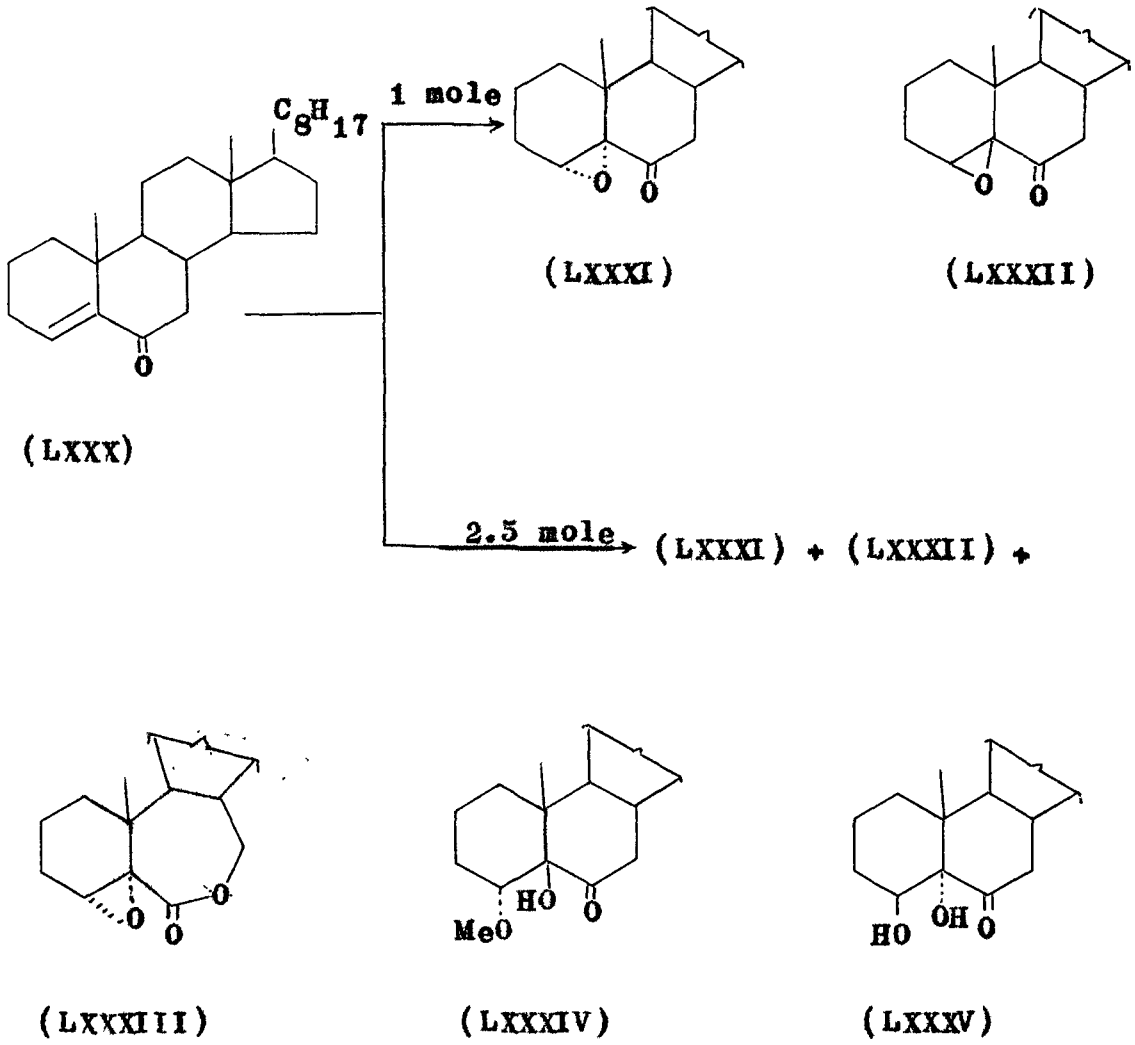
(LXXVIII)



(LXXIX)

The formation of (LXXVII) was of interest in view of the fact that in previous studies on the steroidal 4-en-ones, oxygen insertion invariably occurred between C_3-C_4, thus indicating a greater migratory aptitude of vinylic group relative to a methylene group. It appeared that the presence of a bromine atom at C_6 by some subtle means altered the migratory aptitude of the groups concerned. A similarly constituted γ-lactone acid as (LXXVIII) has been reported earlier.[31]

Ahmad and Siddiqui[33] reported the Baeyer-Villiger oxidation of cholest-4-en-6-one (LXXX) with 1 mole equivalent of perbenzoic acid, using p-toluenesulphonic acid monohydrate as the catalyst and obtained 4α,5-oxido-5α-cholestan-6-one (LXXXI) and 4β-5-oxido-5β-cholestan-6-one (LXXXII). On treatment with an excess of perbenzoic acid (2.5 mole), the ketone (LXXX) produced (LXXXI), (LXXXII) and 4α,5-oxido-7-oxa-8-homo-5α-cholestan-6-one (LXXXIII) along with 5-hydroxy-4α-methoxy-5β-cholestan-6-one (LXXXIV) and 4β,5-dihydroxy-5α-cholestan-6-one (LXXXV), as artefacts of (LXXXII) and (LXXXIII).



(LXXX)

(LXXXI)

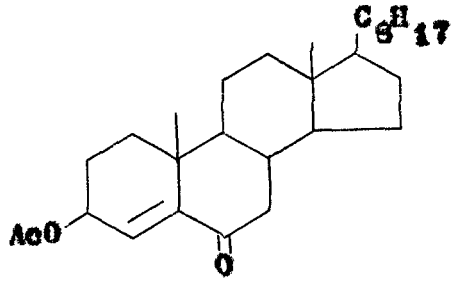
(LXXXII)

(LXXXIII)

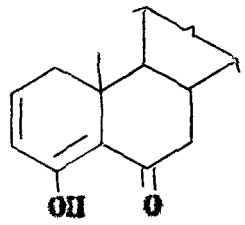
(LXXXIV)

(LXXXV)

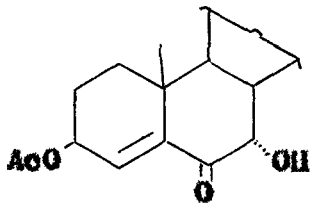
Ahmad and Khan[34,35] performed the reaction of 3β-acetoxycholest-4-en-6-one (LXXXVI) with 1 mole equivalent of perbenzoic acid which afforded 4-hydroxycholesta-2,4-dien-6-one (LXXXVII), 7α-hydroxy-3β-acetoxycholest-4-en-6-one (LXXXVIII), 5-keto-5,6-secocholest-3-en-6-oic acid (LXXXIX) and 3β-acetoxy-6,7-seco-8-formylcholest-4-en-6-oic acid (XC). With an excess of perbenzoic acid, (LXXXVI) gave in addition to (LXXXIX) and (XC), 3β-acetoxy-6,7-secocholest-4-en-5,8-dicarboxylic acid (XCI).



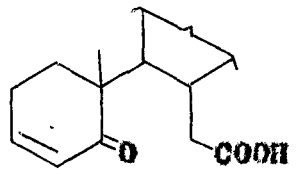
(LXXXVI)



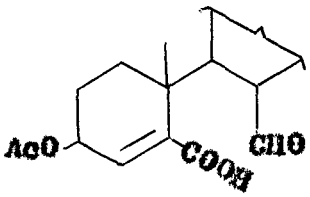
(LXXXVII)



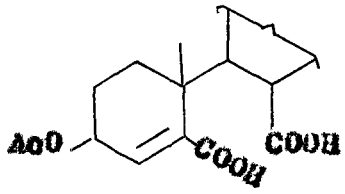
(LXXXVIII)



(LXXXIX)

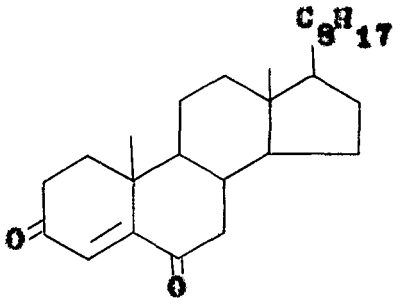


(XC)

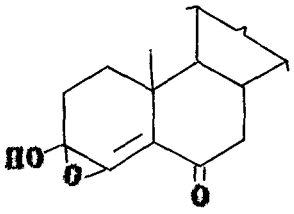


(XCI)

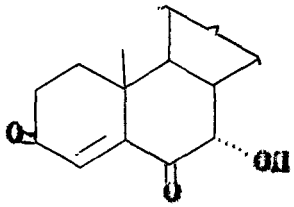
In a very interesting sequence of Baeyer-Villiger oxidation, cholest-4-ene-3,6-dione (XCII) has been shown to afford a novel oxetalactone.[36] The ketone (XCII), with 1 mole equivalent of perbenzoic acid, gave 3-hydroxy-3,4-oxidocholest-4-en-6-one (XCIII), 7α-hydroxycholest-4-ene-3,6-dione (XCIV), and 4-hydroxy-6-methoxycholesta-4,6-dien-3-one (XCV). With 2 mole equivalent of perbenzoic acid, (XCII) yielded (XCIII) and a novel oxetalactone, 5,7aα-oxido-6-oxa-A-homo-5α-cholestane-3,7-dione (XCVI). With 3 mole equivalent, (XCII) afforded (XCVI) and its product of further oxidation, 5,7aα-oxido-3,6-dioxa-A,B-bishomo-5α-cholestane-4,7-dione (XCVII).



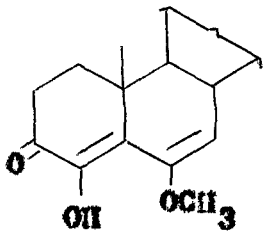
(XCII)



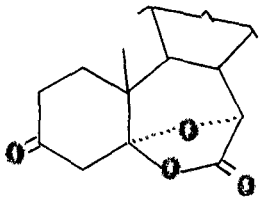
(XCIII)



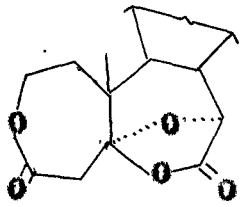
(XCIV)



(XCV)



(XCVI)

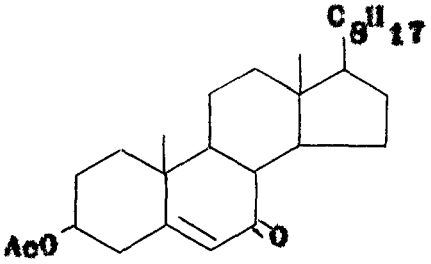


(XCVII)

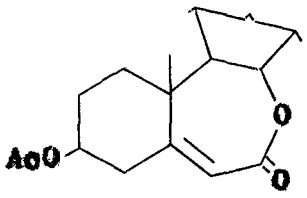
A study or peracid oxidation of easily accessible 3β-acetoxycholest-5-en-7-one (XCVIII) and cholest-5-en-7-one (CIII) was undertaken by Ahmad et al.[37] in view of the fact that in contrast to ring A α,β-unsaturated ketones, no oxidation studies on analogous ring B compounds had been reported till that time.

The ketone (XCVIII) was subjected to Baeyer-Villiger oxidation under varying concentrations of perbenzoic acid using p-toluenesulphonic acid (PTS) or perchloric acid as the catalyst.

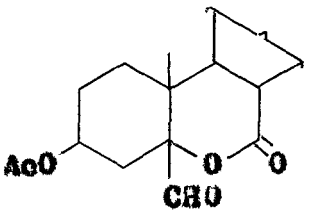
After 84 hours, the ketone (XCVIII) gave 3β-acetoxy-7a-oxa-D-homocholestan-7-one (XCIX), 3β-acetoxy-6-oxa-5-formyl-5β-cholestan-7-one (C) and an inseparable mixture of the seco acids, 3β-acetoxy-5-keto-5,7-seco-6-nor-cholestan-7-oic acid (CI) and 5-keto-5,7-seco-6-norcholest-3-en-7-oic acid (CIII). Interestingly, it was noted that the lactone (XCIX) resulted by the preferential migration of a more highly substituted carbon over vinylic carbon which was in contrast to the general observations[28,38] that a vinylic carbon migrates preferentially. It was inferred from this observation that a more substituted carbon such as C_8 has comparable migratory aptitude relative to a vinylic group.



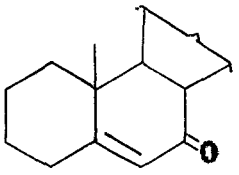
(XCVIII)



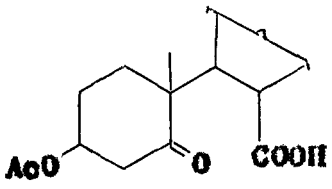
(XCIX)



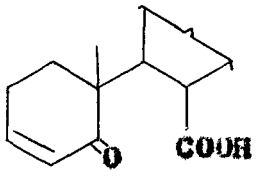
(C)



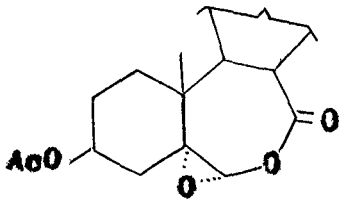
(CII)



(CI)



(CIII)

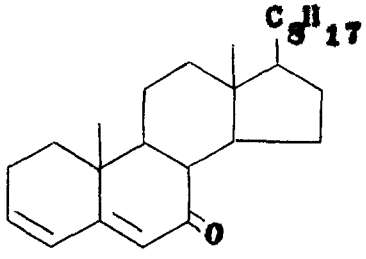


(CIV)

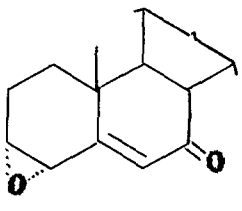
The ketone (CII) under similar conditions of Baeyer-Villiger oxidation afforded the secoacid (CIII).

The formyl derivative (C) and the seco acids (CI) and (CIII) were shown to arise by the acid catalysed rearrangement of the enol lactone (XCIX) as proposed by Pinhey and Schaffner.[28,38] The exclusive formation of (C) and the absence of its 5α-epimer was taken as an evidence that the epoxy oxygen in (CIV) was α-oriented. When the reaction period was extended, only (XCIX) and the mixture of (CI) and (CIII) were obtained. On the other hand, perchloric acid catalysed the oxidation of (XCVIII) giving rise to (XCIX) and the mixture of (CI) and (CIII). It was experimentally substantiated that (XCIX) was not the precursor of (C), (CI) and (CIII).

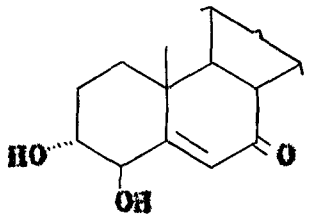
Ahmad et al.[39] carried out the Baeyer-Villiger oxidation of cholesta-3,5-dien-7-one (CV) which furnished 3α,4α-epoxycholest-5-en-7-one (CVI) and its hydrolysed product, 3α,4β-dihydroxycholest-5-en-7-one (CVII) and none of the expected ∈ -lactones.



(CV)

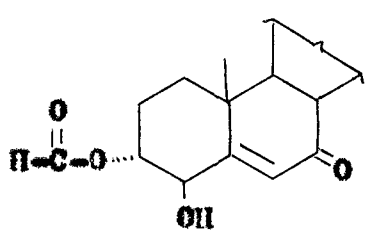


(CVI)

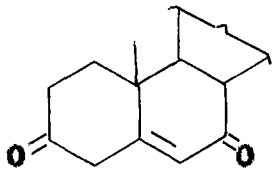


(CVII)

In order to obtain the ϵ -lactone, (CVI) was treated with varying concentrations of perbenzoic acid for different length of time which invariably provided (CVI), (CVII), 3α-formyloxy-4β-hydroxycholest-5-en-7-one (CVIII) and cholest-5-ene-3,7-dione (CIX).

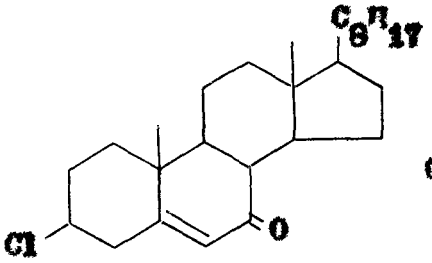


(CVIII)

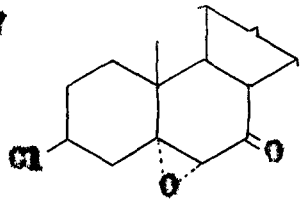


(CIX)

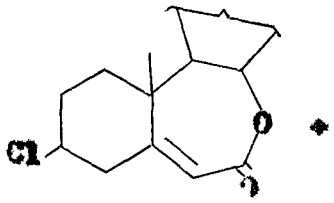
Shafiullah and Khan[40] performed the Baeyer-Villiger oxidation of 3β-chlorocholest-5-en-7-one (CXI) with perbenzoic acid (1 or 2 mole equivalent) in the presence of p-toluenesulphonic acid monohydrate as catalyst and it afforded 3β-chloro-5,6α-oxido-5α-cholestan-7-one (CXI), 3β-chloro-7a-oxa-8-homocholest-5-en-7-one (CXII), 3β-chloro-5-formyl-6-oxa-5α-cholestan-7-one (CXIII) and 3β-chloro-5-oxo-5,7-seco-6-norcholestan-7-oic acid (CXIV). With 3 mole equivalent, (CX) provided, in addition to (CXI-CXIV), 5-oxo-5,7-seco-6-norcholest-3-en-7-oic acid (CXV).



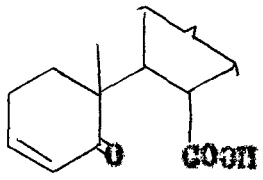
(CX)



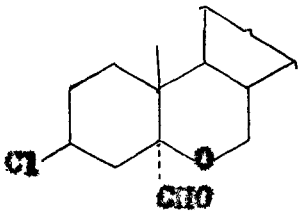
(CXI)



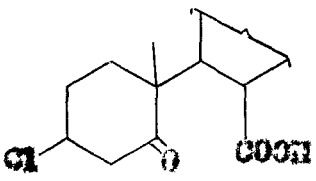
(CXII)



(CXV)

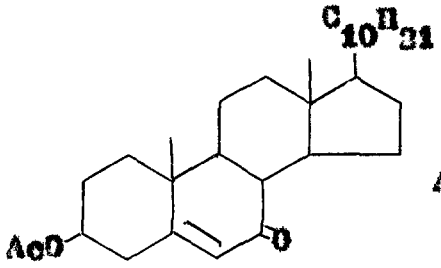


(CXIII)

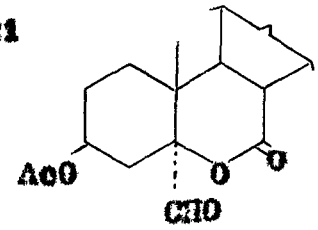


(CXIV)

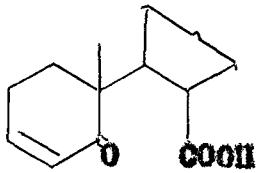
Some easily accessible α,β-unsaturated ketones in the stigmastane series have been subjected to Baeyer-Villiger oxidation conditions in order to get analogous products as obtained in the case of cholestane series. However, for that matter, 3β-acetoxystigmast-5-en-7-one (CXVI) under similar conditions yielded formyl lactone (CXVII) and the nor-seco acid (CXVIII).[41] It could be noted that contrary to the previous reaction of (CXVIII), the 5α-formyl derivative (CXVII) was obtained in this case.



(CXVI)

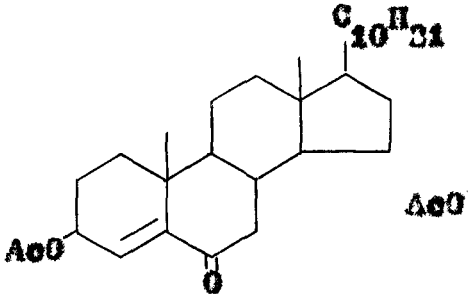


(CXVII)

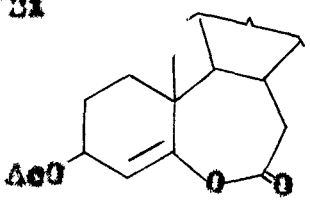


(CXVIII)

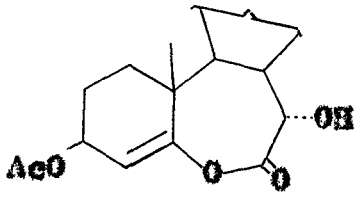
The oxidation of 3β-acetoxystigmast-4-en-6-one (CXIX) produced the enol lactone, 3β-acetoxy-6-oxa-B-homostigmast-4-en-7-one (CXX) and 7aα-hydroxy-3β-acetoxy-6-oxa-B-homostigmast-4-en-6-one (CXXI).[42]



(CXIX)



(CXX)

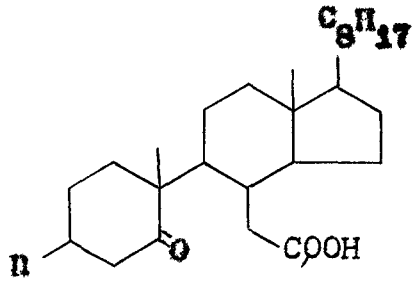


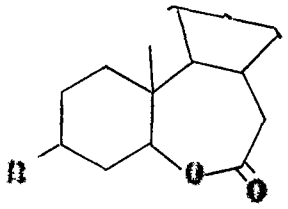
(CXXI)

Baeyer-Villiger oxidation of secoketones

It has been shown that the seco-acids, 3β-acetoxy-5-keto-5,6-secocholestan-6-oic acid (CXXII) and 5-keto-3,6-secocholestan-6-oic acid (CXXIII) when heated under reflux

with acetic anhydride and fused sodium acetate afforded 3β-acetoxy-6-oxa-8-homocholest-4-en-7-one (CXXIV) and 6-oxa-8-homocholest-4-en-7-one (CXXV) respectively.[41]

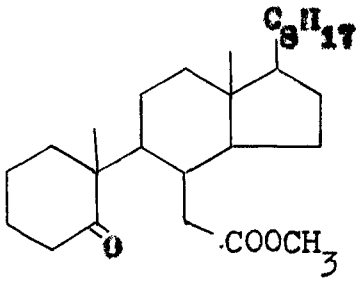


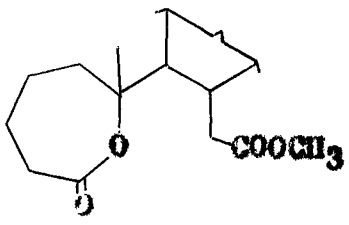


(CXXII) R, OAc
(CXXIII) R, H

(CXXIV) R, OAc
(CXXV) R, H

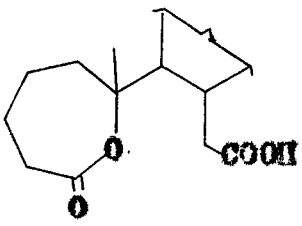
Ahmad and Waris[44] reported the perbenzoic acid oxidation of methyl 5-keto-3,6-secocholestan-6-oate (CXXVI) which gave lactones (CXXVII) and (CXXVIII). Methyl 5-keto-5,6-secocholestan-3-en-6-oate (CXXIX) under similar conditions, provided methyl 3α,4α-epoxy-5-keto-3,6-secocholestan-6-oate (CXXX) and methyl 5,6-seco-3α,4α-epoxy-5-keto-5a-oxa-A-homocholestan-6-oate (CXXXI).



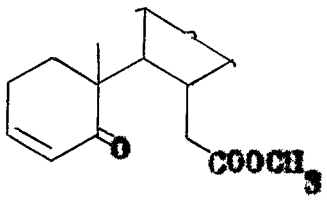


(CXXVI)

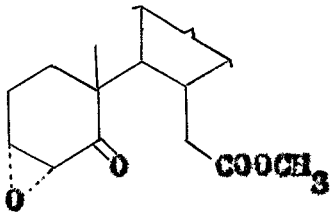
(CXXVII)



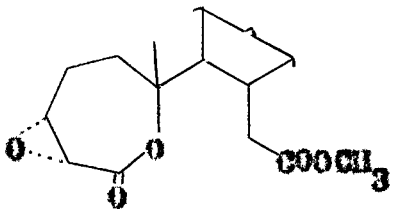
(CXXVIII)



(CXXIX)



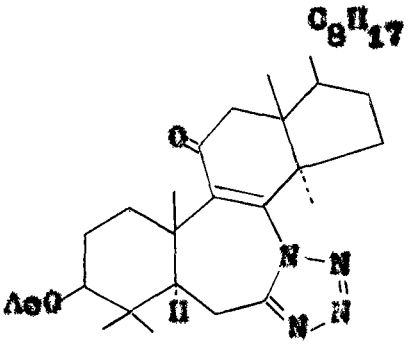
(CXXX)



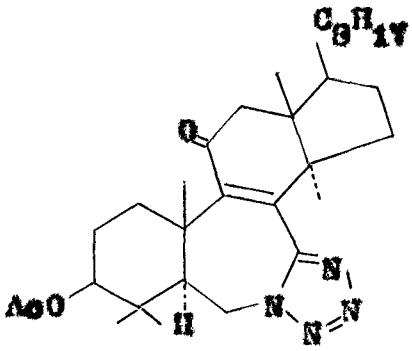
(CXXXI)

Steroidal Tetrazoles

Steroidal compounds consisting of a five membered doubly unsaturated heterocycle with one carbon and four nitrogen atoms are termed as tetrazolosteroids. Probably the first example of the formation of a tetrazole in steroid and terpenoid field was given by Barnes et al.[46] in 1953. They reported the formation of a tetrazole (CXL) or (CXLI), the structure, however, was not firmly established at that time.



(CXL)

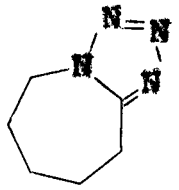


(CXLI)

Benson[40] has given an excellent review touching upon almost every aspect of tetrazole chemistry.

Tetrazoles enjoy important biological as well as non-biological applications. These have been applied in various explosives and in propellants. Various tetrazole salts have been claimed for use in primers. They are of use in fibre, dyestuff and textile industries and have applications in

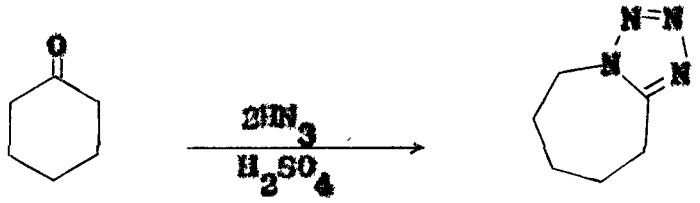
photography also. On the biological side, the best known is pentamethylene tetrazole (Metrazole) (CXLIII) which is a potent stimulant of the central nervous system and is used clinically to counteract intoxication due to over dosage of barbiturates.[47] Stimulant, depressant, sedative and analgesic activities are shown by certain tetrazoles. Anti convulsant, hypotensive and andronergic blocking action is exhibited by a number of 5-mono-substituted tetrazoles.[40]



(CXLIII)

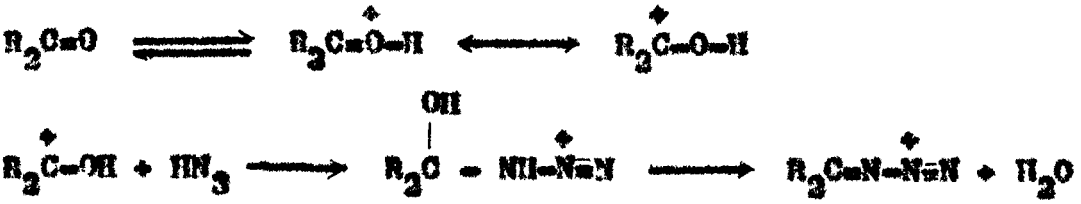
Organic chemists, realising the above mentioned applications, directed their efforts towards the synthesis of tetrazoles. One of the most valuable methods discovered by Schmidt[48] for the preparation of tetrazoles is the rearrangement reaction between ketones and hydrazoic acid in the presence of strong acids. When one mole of hydrogen azide reacts with one mole of a carbonyl compound, N-substituted amides are formed; with two or more moles of hydrogen azide, tetrazoles are formed. The reaction has found its most extensive application with cyclic ketones with which yields are generally better than with acyclic ketones.

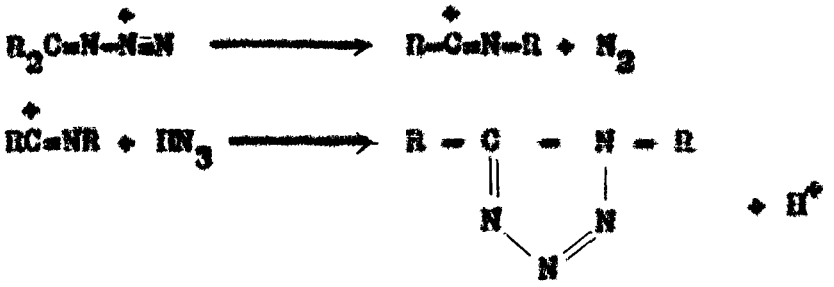
Pentamethylene tetrazole (Metrazole) (CXLIII) may be obtained from cyclohexanone (CXLII) by this procedure.[49]



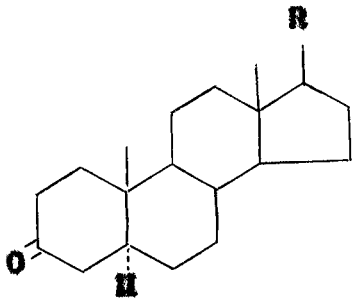
(CXLII) (CXLIII)

Smith[50] has advanced a probable mechanism for this transformation. The first step is the conversion of the carbonyl compound to a carbonium ion under the influence of the acid catalyst. This is followed by combination with one molecule of hydrazoic acid (functioning as a base), dehydration of the intermediate and rearrangement to an imidocarbonium ion, with simultaneous loss of nitrogen. When tetrazole formation occurs, a second molecule of hydrazoic acid reacts with the imidocarbonium ion, the positive charge being lost as a proton. Combination of hydrogen azide with the imidocarbonium ion to form a tetrazole competes with reaction of the imidocarbonium ion with water to form an N-substituted amide. This mechanism accounts satisfactorily for the necessity of using strong acid as catalyst.

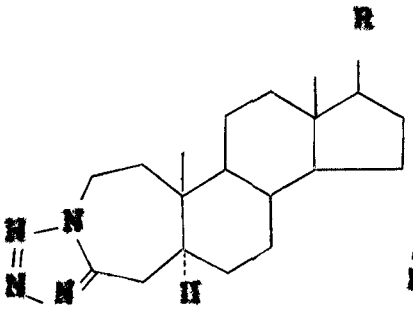




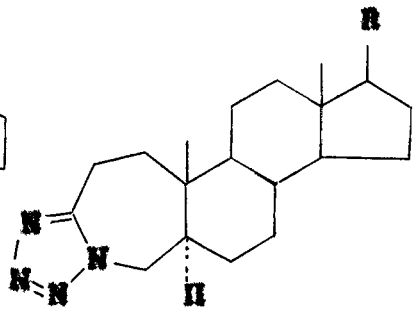
Steroidal tetrazoles did not attract the attention of synthetic organic chemists until 1963 when Hechoulam[51] reported the synthesis of a number of ring A fused steroidal tetrazoles and claimed that some of them possessed antifertility and anti-spermatogenic activity. Hechoulam subjected 5α-cholestan-3-one (CXLIV) and 17β-hydroxy-5α-androstan-3-one (CXLV) to Schmidt reaction using excess of hydrazoic acid and obtained mixtures of isomeric tetrazoles (CXLVI, CXLVII) and (CXLVIII, CXLIX), respectively, containing 3-aza-A-homo [3,4-d] tetrazole and 4-aza-A-homo [3,4-d] tetrazole system.



(CXLIV) R, C_8H_{17}
(CXLV) R, OH

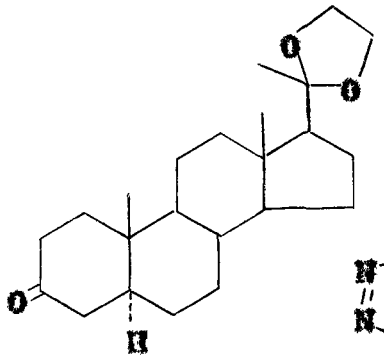


(CXLVI) R, C_8H_{17}
(CXLVII) R, OH

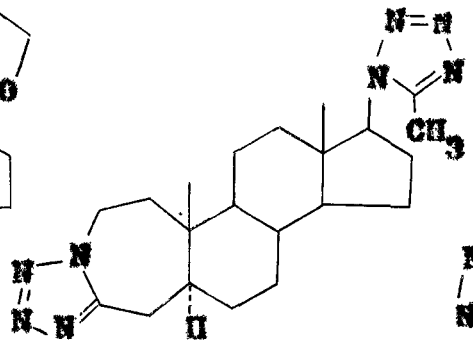


(CXLVIII) R, C_8H_{17}
(CXLIX) R, OH

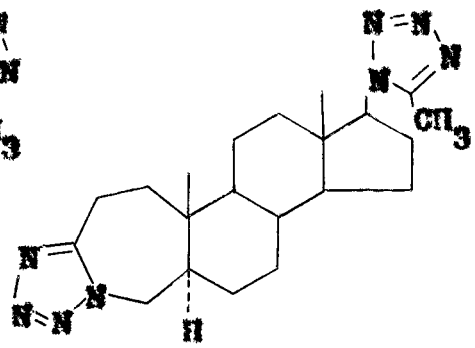
20,20-Ethylenedioxy-5α-pregnan-3-one (CL), under similar conditions afforded a mixture of 17β-(5-methyl tetrazol-1-yl)-3-aza-A-homo-5α-androstano [3,4-d] tetrazole (CLI) and its 4-aza-isomer (CLII). The acetal ring at C_{20} is hydrolysed under acidic conditions to C_{20} ketone which reacts further with hydrazoic acid to form the tetrazole at 17-position.[51]



(CL)



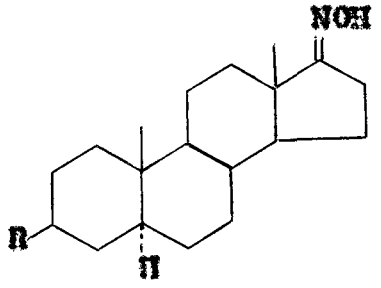
(CLI)



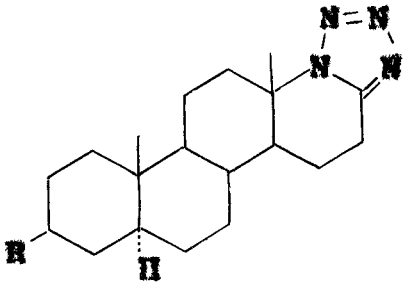
(CLII)

The realisation of the pharmacological potential of steroidal tetrazoles prompted the organic chemists towards their synthesis and subsequently several papers appeared concerning their synthesis and biological activity. Crabbe et al.[53] of Syntex group reported the formation of ring D fused tetrazoles from the reaction of 17-ketoximes with excess of sodium azide in the presence of sulphuric acid. The reaction of 17-hydroximino-5α-androstane (CLIII) was shown to afford the tetrazole, 17a-aza-D-homo-5α-androstane [17a,17-d] tetrazole (CLIV) and the

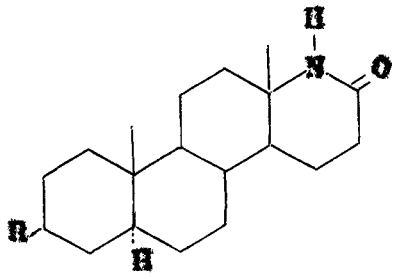
D-homolactam (CLV). Similarly, the oxime (CLVI) yielded 3β-acetoxy-17a-aza-D-homo-5α-androstano [17a,17-d] tetrazole (CLVII) and the lactam (CLVIII) while the oxime (CLIX) was shown to furnish the tetrazole, 17a-aza-3-hydroxy-D-homoestra-1,3,5(10)-triene [17a,17-d] tetrazole-3-methyl ether (CLX) along with the seco-nitrile (CLXI) and the lactam (CLXII).



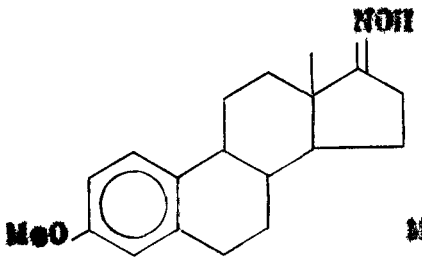
(CLXIII) R, H
(CLVI) R, OAc



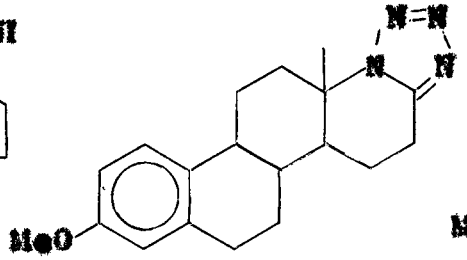
(CLXIV) R, H
(CLVII) R, OAc



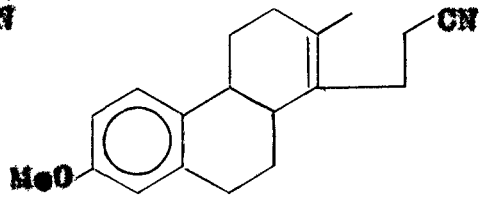
(CLV) R, H
(CLVIII) R, OAc



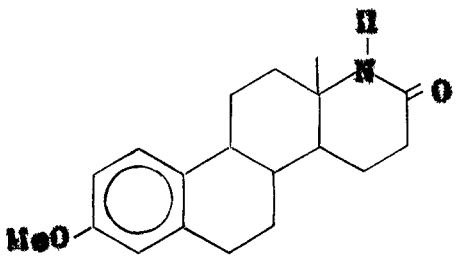
(CLIX)



(CLX)

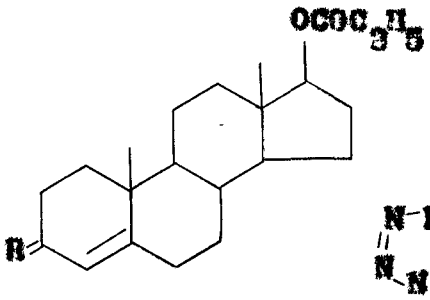


(CLXI)

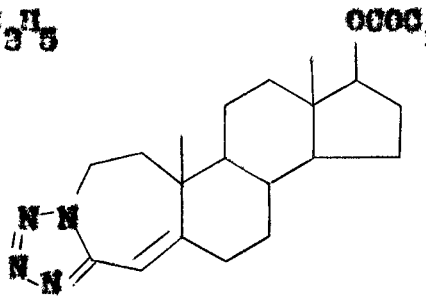


(CLXII)

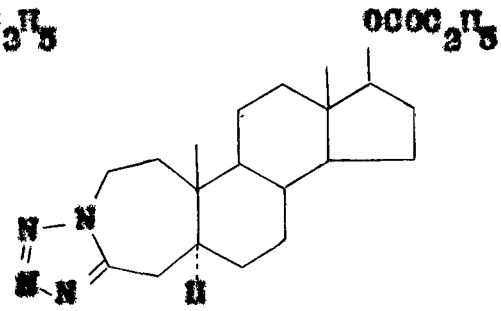
Moural and Syhora[53] reported the synthesis of a series of 3-aza-A-homo-4a-eno [3,4-d] tetrazole analogues from the corresponding 3-oxo-4-enosteroids from their reaction with hydrazoic acid. The reaction of 3-oxo-androst-4-en-17β-propionate (LXXIII) has been reported to yield the tetrazole (CLXIII) which on hydrogenation gave the corresponding dihydro derivative (CLXIV). The tetrazole (CLXIII) was also obtained when 3-hydroximinoandrost-4-en-17β-propionate (CLXIVa) was treated with hydrazoic acid. Similarly, 3-oxocholest-4-ene (LI) was shown to furnish 3-aza-A-homocholest-4a-eno [3,4-d] tetrazole (CLXV).



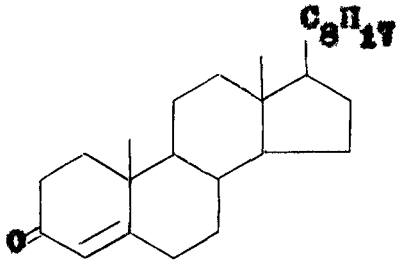
(LXXIII) R, O
(CLXIVa) R, NOH



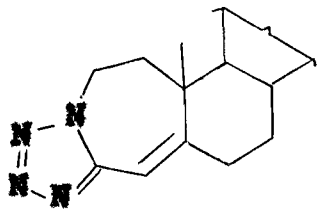
(CLXIII)



(CLXIV)

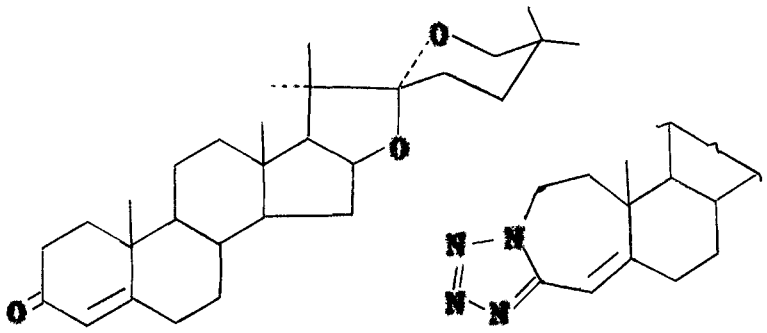


(LI)



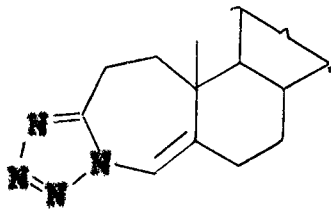
(CLXV)

In 1972, a number of ring A,B and D fused steroidal tetrazoles were reported by Harkishan Singh and coworkers.[54] Keeping in view the pharmacological effect of tetrazosteroids, Singh et al.[54] treated (25R)-spirost-4-en-3-one (CLXVI) with excess of hydrazoic acid in the presence of boron trifluoride-etherate and obtained a tetrazole, 3-aza-A-homo-(25R)-spirost-4a-eno [3,4-d] tetrazole (CLXVII) in preference to the alternative 4-aza-structure (CLXVIII) on the basis of spectral characteristics and the observation that Schmidt reaction of 4-en-3-ones or Beckmann rearrangement of their oximes generally yield lactams corresponding to 3-aza-A-homo-4a-eno-4-one system.[55]



(CLXVI)

(CLXVII)



(CLXVIII)

Survey of the literature reveals that in the recent past various steroidal tetrazoles have been reported by different authors. The spectral characteristics of a number of steroidal tetrazoles are tabulated below (Table 1).

Table - 1

Spectral data of some tetrazolosteroids

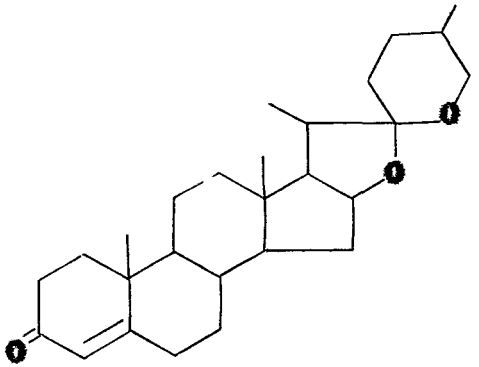
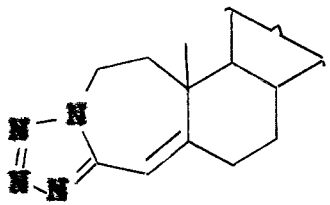
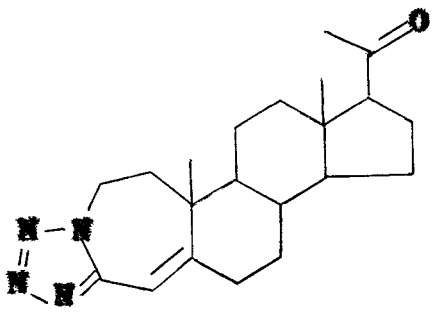
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm (log ϵ)	Ref.
 (CLXVI)	 (CLXVII)	6.49s (C_{4a}-H), 4.50m (C_3-H_2) 1.37s (C_{10}-Me); 1630 (C=C), 1530, 1450, 1380 (C=N, N=N)	243 (4.23)	54
(CLXVI)	 (CLXIX)	6.50s (C_{4a}-H), 4.50s (C_3-H_2); 1660 (C=C), 1520, 1445, 1375 (C=N, N=N)	241 (4.41)	54

Table - 1 (Contd.)

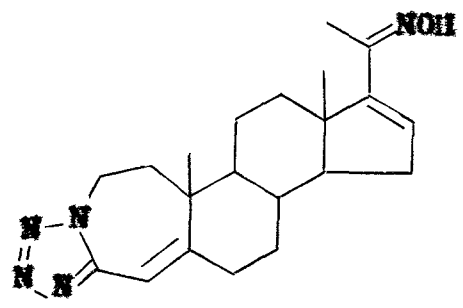
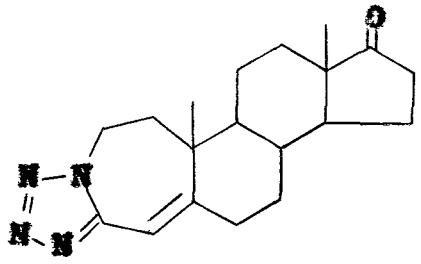
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
(CLXVI)	 (CLXX)	0.51s (C_{18}-H), 4.51m (C_2-H_2); 1648 (C=C), 1530, 1445, 1375 (C=N, N=N).	240 (4.17)	54
(CLXVI)	 (CLXXI)	0.50s (C_{18}-H), 4.50m (C_2-H_2); 1650 (C=C), 1530, 1445, 1395 (C=N, N=N).	242 (4.23)	54

Table - 1 (Contd.)

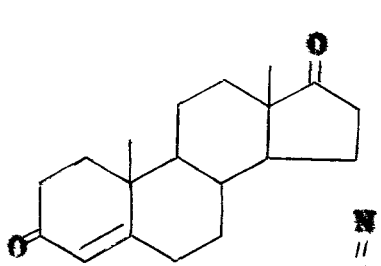
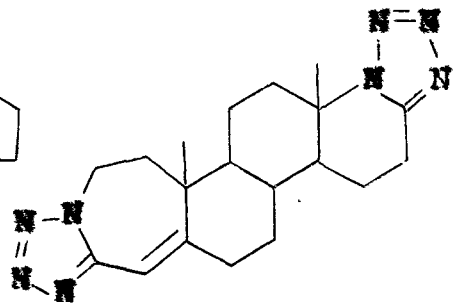
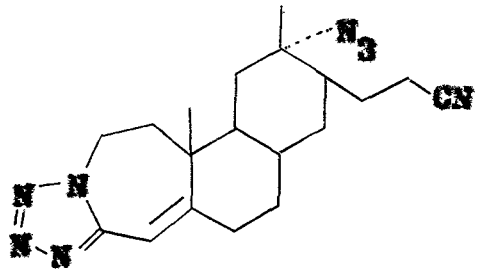
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm ($10^3 \epsilon$)	Ref.
 (CLXXI)	 (CLXXIII)	0.59s (C_{4a}-H), 4.55m (C_2-H_2), 3.0m (C_{10}-H_3); 1650 (C=C), 1530, 1450 (C=N, N=N).	242 (4.25)	56.57
(CLXXII)	 (CLXXIV)	0.57s (C_{4a}-H), 4.56m (C_2H_2), 3.49m (NC-C_{16}-H_2); 2250 (CN), 2095 (N_3), 1650 (C=C), 1530, 1450 (C=N, N=N).	243 (4.23)	56.57

Table - 1 (Contd.)

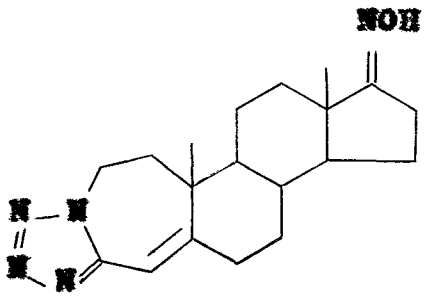
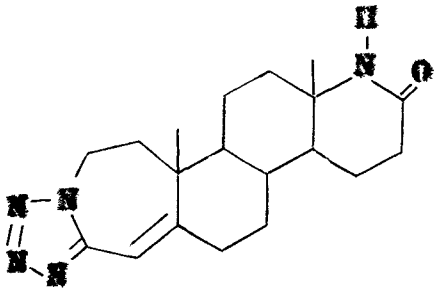
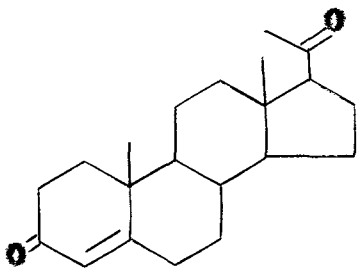
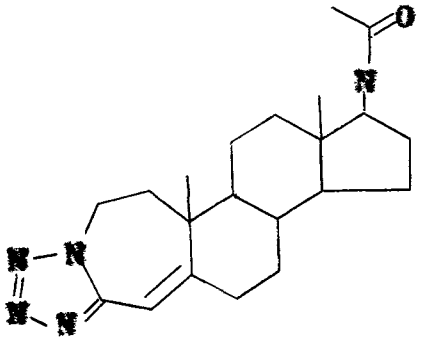
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R. (cm^{-1})	U.V. mμ ($\log\epsilon$)	Ref.
 (CLXXV)	 (CLXXVI)	6.50s (C_{4a}-H), 4.50m (C_3-H_2); 3450, 3125 (NH), 1660 (CONH), 1650 (C=C), 1530, 1450, 1385 (C=N, N=N).	240 (4.21)	58
 (CLXXVII)	 (CLXXVIII)	6.50s (C_{4a}-H), 4.45m (C_3-H_2), 3.92m (C_{17}-αH), 1.97s (-NHCO-Me); 3335 (NH), 1670 (CONH), 1650 (C=C), 1530, 1450, 1375 (C=N, N=N).	243 (4.23)	59

Table - 1 (Contd.)

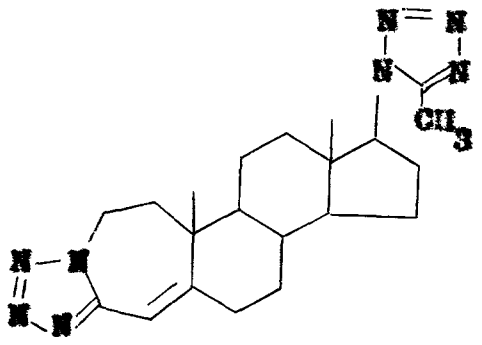
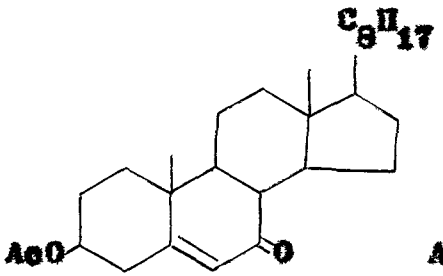
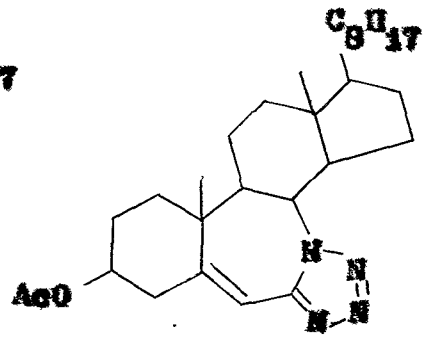
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. mμ (log ε)	Ref.
(CLXXVII)	 (CLXXIX)	6.51s (C_{4a}-H), 4.50m (C_2-H_2), 4.15m (C_{17}-αH), 2.54s (CH_3-C=N); 1650 (C=C), 1520, 1450, 1300 (C=C, N=N).	243 (4.23)	59
 (CXVI)	 (CLXXX)	6.02s (C_6-H), 4.75m (C_3-αH), 4.25m (C_3-βH), 2.05s ($\underline{CH}_3$-COO); 1735 (CH_3-COO), 1665 (C=C), 1505, 1465, 1370 (C=C, N=N), 1243 (Acetate).	241 (4.00)	59

Table - 1 (Contd.)

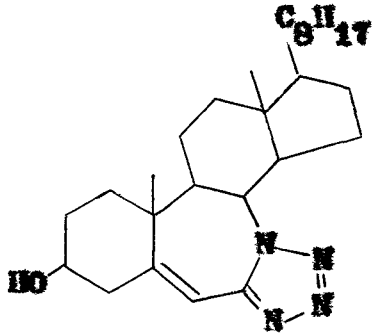
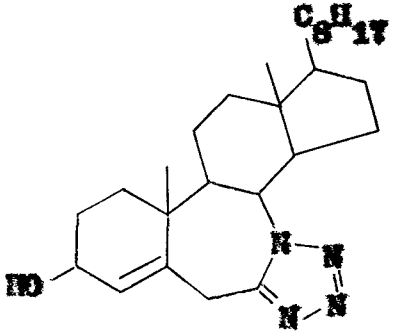
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
(CXVI)	 (CLXXXI)	0.63s (C_{18}-H), 3.75m (C_3-αH), 4.25m (C_8-βH), 2.12br (OH ; D_2O exchangeable); 3310br (OH), 1663 (C=C), 1510, 1463, 1380, 1373 (C=N, N=N).	245 (4.06)	59
(CXVI)	 (CLXXXII)	5.68d (C_4-H; J=3.5 Hz), 4.35m (C_8-βH), 4.03m (C_3-αH), 3.72br (C_6-H_2); 3360br (OH), 1530, 1465, 1389, 1370 (C=N, N=N).	-	59

Table - 1 (Contd.)

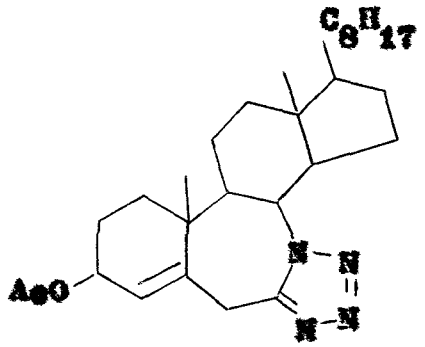
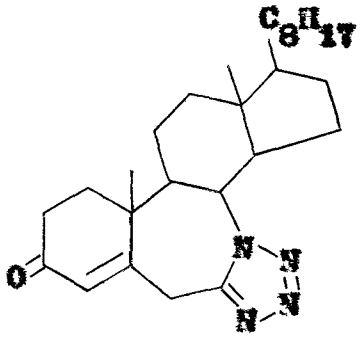
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
(CXVI)	 (CLXXXIII)	5.03d (C_4-H; J=3.3 Hz), 5.03m (C_3-αH), 4.38m (C_8-βH), 3.72br (C_6-H_2), 2.03s (CH_3COO); 1735 (CH_3-C-O), 1530, 1460, 1330, 1370 (C=N, N=N), 1245 (Acetate).	-	59
(CXVI)	 (CLXXXIV)	5.69s (C_4-H), 4.55m (C_8-βH), 4.05br (C_6-H_2), 1.17s (C_{10}-Me), 0.83s (C_{13}-Me); 1675 (C=C-C=O-), 1625 (C=C), 1530, 1462, 1337 (C=N, N=N).	235 (4.14)	59

Table - 1 (Contd.)

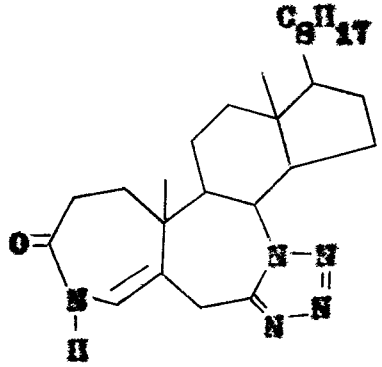
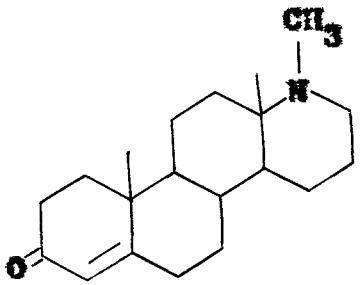
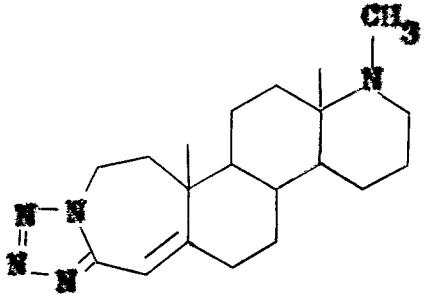
Starting Ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm ($log_{10}\epsilon$)	Ref.
(CLXXXIV)	 (CLXXXV)	7.17d (NH; D_2O exchangeable), 5.81d (C_4-H; J=6 Hz), 4.45m (C_8-βH), 3.68br (C_6-H_2); 3220, 3111 (NH), 1667 (CONH), 1536, 1460, 1418, 1379 (C=N, N=N).	246 (4.09)	60
 (CLXXXVI)	 (CLXXXVII)	6.52s (C_{4a}-H), 4.50m (C_3-H_2), 2.19s (N-CH_3); 1652 (C=C), 1528, 1440, 1320 (C=N, N=N).	243 (4.23)	61

Table - 1 (Contd.)

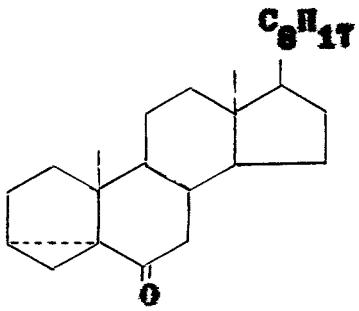
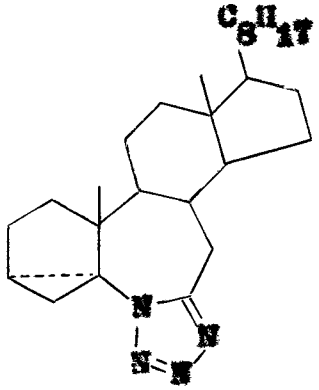
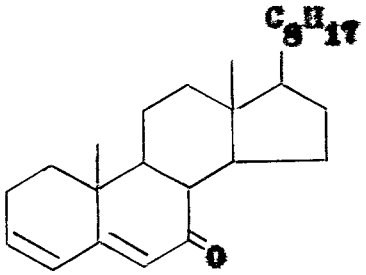
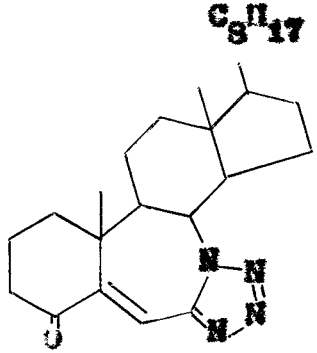
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm (log ∈)	Ref.
 (XVII)	 (CLXXXVIII)	3.36 (C_{7a}-H_2), 0.96s (C_{10}-Me), 0.66s (C_{13}-Me); 3030 (cyclopropane), 1535, 1460, 1365 (C=N, N=N).	-	62
 (CV)	 (CLXXXIX)	7.53s (C_6-H), 4.5br (C_8-βH), 3.5m (C_3-H_2); 1650 (C=C-C(=O)-C), 1500, 1465, 1360 (C=N, N=N).	-	62

Table - 1 (Contd.)

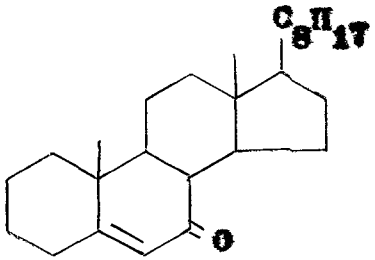
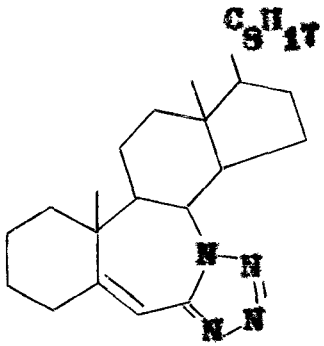
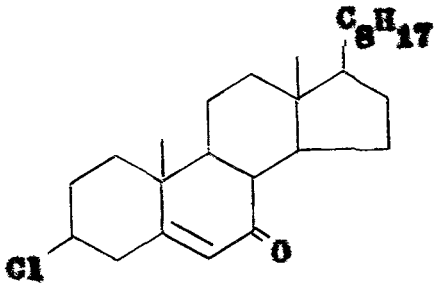
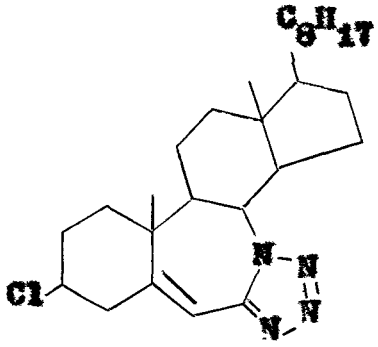
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. mm ($log \epsilon$)	Ref.
 (CII)	 (CXL)	0.55s (C_6-H), 4.32br (N-C_8-H); 1670 (C=C), 1505, 1465, 1390 (C=N, N=N).	243 (4.10)	62
 (CX)	 (CXLI)	0.63s (C_6-H), 4.31br (N-C_8-H), 3.81br (C_3-αH; J=22 Hz); 1660 (C=C), 1505, 1470, 1380 (C=N, N=N).	240 (4.13)	62

Table - 1 (Contd.)

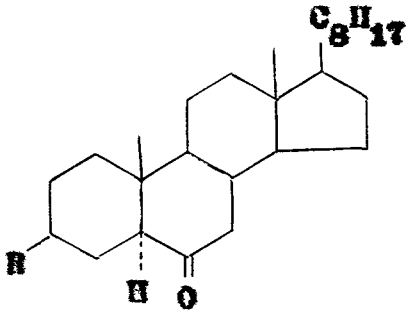
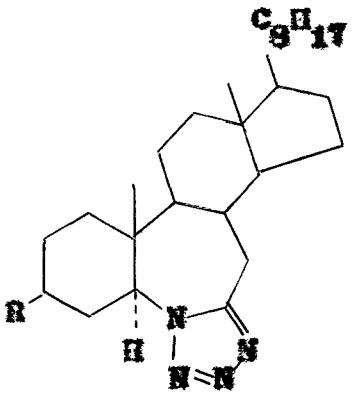
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R. (cm^{-1})	U.V. nm (log ∈)	Ref.
 (VIII) R, H (VIV) R, OAc (XVIII) R, Cl (CXLV) R, OH	 (CXLII) R, H (CXLIII) R, OAc (CXLIV) R, Cl (CXLVI) R, OH	(CXLII) R, H 4.26dd (C_5-H; JC_5-αH, C_6-βH, J=10 Hz, C_5-αH; C_6-αH= 7 Hz), 3.21d (C_{7a}-Hx, JC_{7a}-Hx; C_{7a}-Hy=15 Hz); 0.43s (C_{13}-Me), 0.90, 0.91, 0.63 (remaining methyls); 1540, 1460, 1390 ($C=N$, $N=N$).	-	63
		(CXLIII) R, OAc 4.78br (C_3-αH), 4.45dd (C_5-H; J=14 and 7 Hz), 3.4d (C_{7a}-H; J=15 Hz), 2.06s (CH_3-COO); 0.55s (C_{13}-CH_3), 0.91, 0.83, 0.65 (methyls); 1720 (CH_3COO), 1525, 1455, 1360 ($C=N$, $N=N$).	-	63

Table - 1 (Contd.)

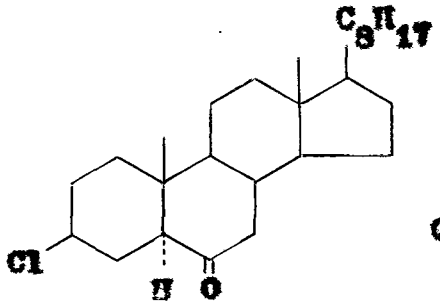
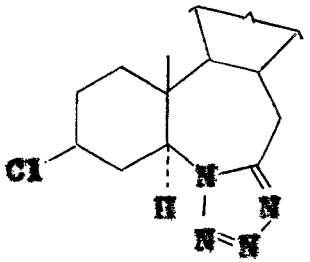
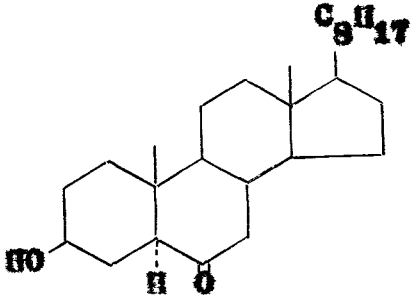
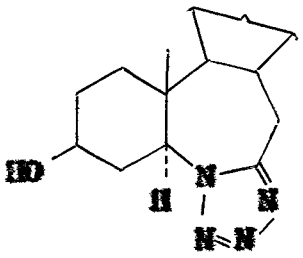
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
 (XVIII)	 (CXLIV)	4.66 dist.dd (C_5-H and C_3H; J=10 and 6 Hz), 3.4d (C_{7a}-H; J=15 Hz), 0.53s (C_{13}-CH_3), 0.93, 0.83, 0.66 (methyls); 1540, 1470, 1380 (C=N, N=N).	-	63
 (CXLV)	 (CXLVI)	4.33dd (C_5-H; J=12 and 7 Hz), 3.75br (C_3-H), 3.39d (C_{7a}-H; J=15 Hz), 0.52s (C_{13}-CH_3), 0.91, 0.81, 0.63 (methyls); 3400br (OH), 1540, 1480, 1390 (C=N, N=N).	-	63

Table - 1 (Contd.)

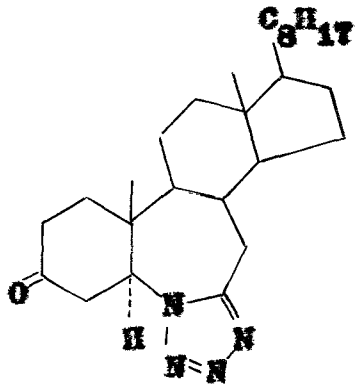
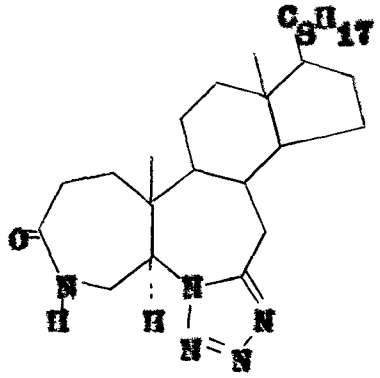
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R. (cm^{-1})	U.V. nm (log ε)	Ref.
(CXLVI)	 (CXLVII)	4.60dd (C_5-H, J=13 and 6 Hz), 3.5m (C_{7a}-H_2), 0.68s (C_{13}-CH_3), 0.91, 0.81, 0.73 (methyls); 1732 (C=O), 1530, 1460, 1360 (C=N, N=N).	-	63
(CXLVII)	 (CXLVIII)	7.0br (NH, D_2O exchangeable), 4.66br (C_5-H), 4.06m (C_{4a}-H_2), 3.41m (C_{7a}-H_2), 0.45s (C_{13}-CH_3), 0.91, 0.81, 0.65 (methyls); 3340, 3300 (NH), 1690, 1640 (CONH), 1540, 1470, 1380 (C=N, N=N).	-	63

Table - 1 (Contd.)

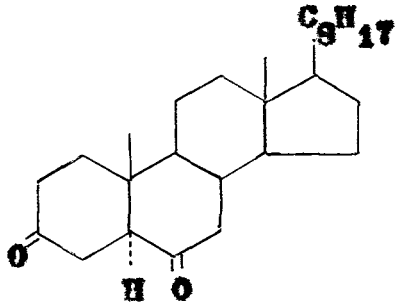
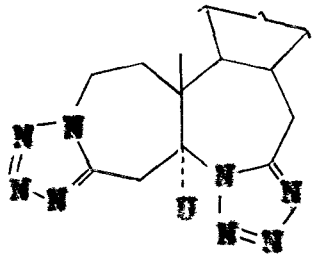
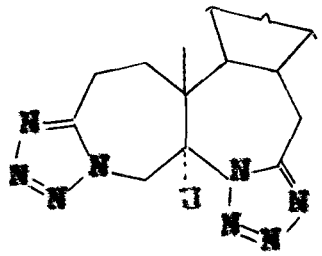
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
 (CXLIX)	 (CC)	4.93d ($C_5-\alpha\frac{1}{2}H$; J=7 Hz), 4.49m ($C_5-\alpha\frac{1}{2}H$, C_3-H_2, $C_{4a}-H_{eq}$), 4.0d ($C_{4a}-H_{ax}$; J=10 Hz), 3.36d ($C_{7a}-H$; J=15 Hz); 1535, 1465, 1380 (C=N, N=N).	-	64
(CXLIX)	 (CCI)	5.49 dist.d($C_5-\alpha H$; J_{aa}=10 Hz; J_{ae}=6 Hz), 5.0d ($C_{4a}-H_2$, major, J=10 Hz), 3.55d ($C_{7a}-H$, J=15 Hz), 3.13m (C_3-H_2); 1540, 1470, 1390 (C=N, N=N).	-	64

Table - 1 (Contd.)

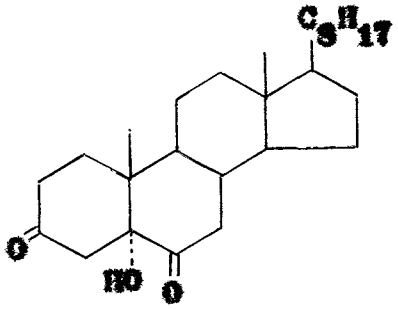
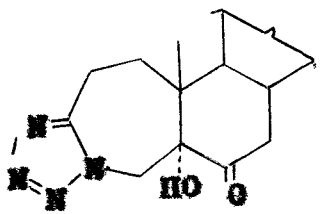
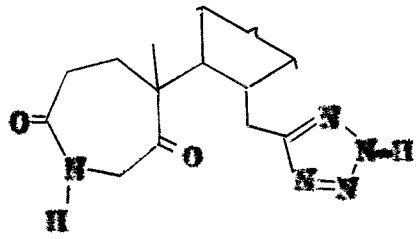
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R. (cm^{-1})	U.V. nm (log ∈)	Ref.
 (CCII)	 (CCIII)	5.05 and 4.41d (C_{4a}-H_2; J=10 Hz) 3.25m (C_3-H_2); 3400, 3300br (OH), 1715 (C=O), 1545, 1490, 1390 (C=N, N=N).	-	64
(CCII)	 (CCIV)	6.8br (CONH), 4.03m (C_6-H_2), 3.3br (C_7-H_2), 3.3m (C_2-H_2), 1.1 (C_{13}-CH_3), 0.88, 0.80, 0.63 (methyls); 3350, 3340 (NH of amine), 3360br (NH of lactam), 1750 (C=O), 1630 (CONH), 1570, 1490, 1390 (C=N, N=N).	-	64

Table - 1 (Contd.)

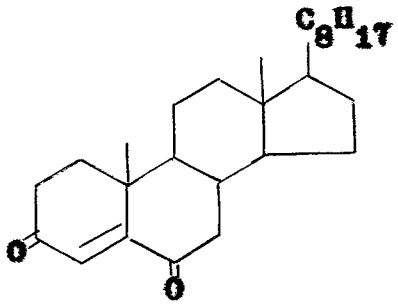
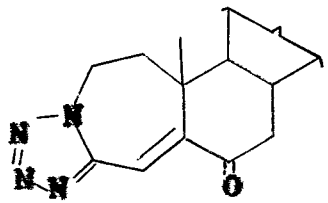
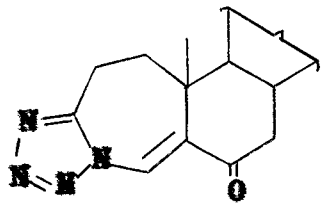
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. mm (log ϵ)	Ref.
 (XCII)	 (CCV)	7.13s (C_{4a}-H), 4.56m (C_3-H_2); 1690 (C=C-C=O), 1520, 1460, 1380 (C=N, N=N).	260 (4.38)	64
(XCII)	 (CCVI)	7.8s (C_{4a}-H), 3.26m (C_3-H_2); 1690 (C=C-C=O), 1620 (C=O), 1520, 1455, 1380 (C=N, N=N).	243 (4.1)	64

Table - 1 (Contd.)

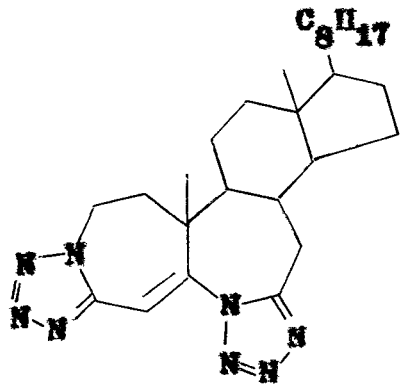
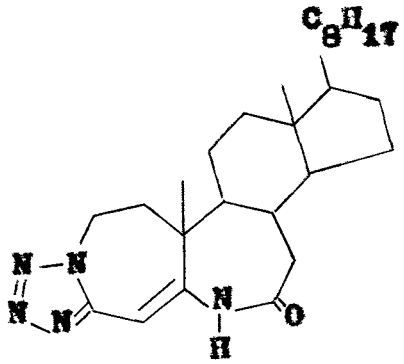
Starting ketone(s)	Product(s)	N.M.R. (δ) and I.R. (cm^{-1})	U.V. nm (log ϵ)	Ref.
(XCII)	 (CCVII)	7.03s (C_{4a}-H), 4.68m (C_2-H_2), 3.45d (C_{7a}-H, J=15 Hz); 3060w (C=C-H), 1670s (C=C), 1530, 1460, 1375 (C=N, N=N)	245 (4.4)	64
(XCII)	 (CCVIII)	8.56br,s (CONH), 6.8s (C_{4a}-H), 4.58m (C_2-H_2); 3220 (NH), 1675, 1655 (CONH), 1640 (C=C), 1530, 1455, 1375 (C=N, N=N).	243 (4.1)	64

Table - 1 (Contd.)

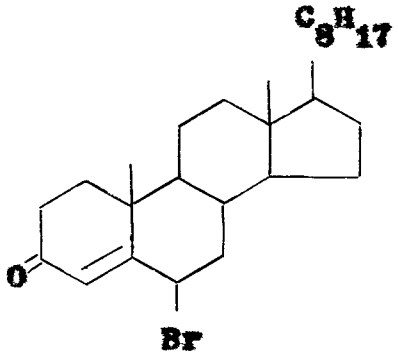
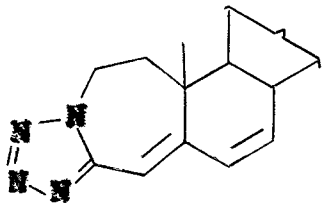
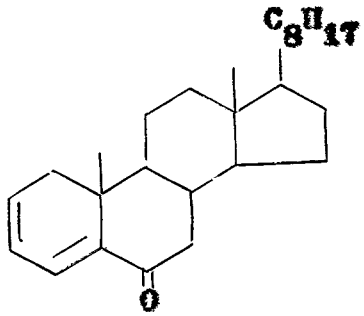
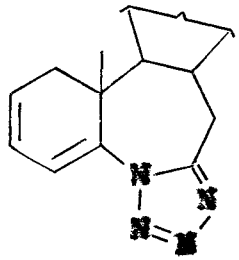
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R. (cm^{-1})	U.V. nm ($log \epsilon$)	Ref.
 (LXXVI)	 (CCIX)	6.30s (C_{4a}-H), 6.03m (C_6-H and C_7-H), 4.51m (C_2-H_2); 1650 (C=C), 1537, 1475, 1390 (C=N, N=N).	287 (4.47)	64
 (CCX)	 (CCXI)	6.61s (C_4-H), 6.05m (3H, C_2-H, C_3-H, C_4-H), 3.24d (C_{7a}-H; J=15 Hz), 0.9s (C_{10}-Me), 0.7 (C_{13}-Me); 1650 (C=C), 1550, 1510, 1460, 1375 (C=N, N=N).	280 (ϵ10200)	65

Table - 1 (Contd.)

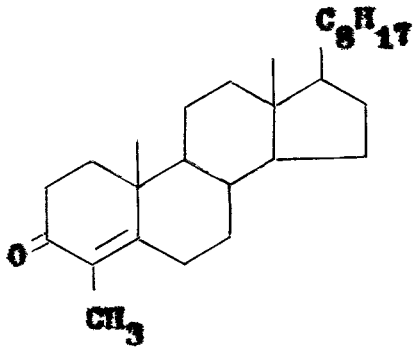
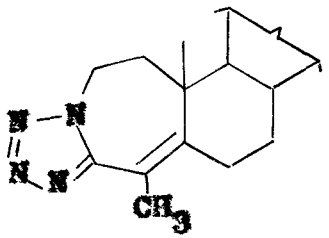
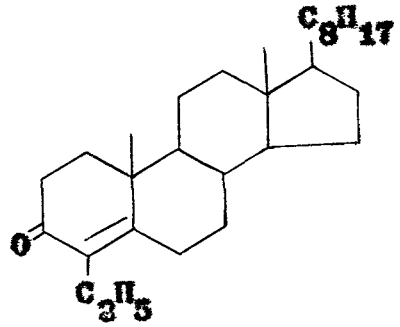
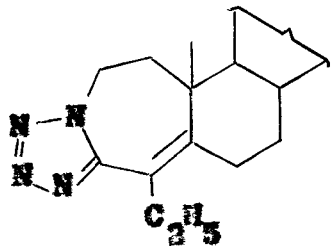
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm (log∈)	Ref.
 (CCXII)	 (CCXIII)	4.33τ (C_3-H_2), 3.13s (C_{4a}-CH_3), 0.98, 0.88 (methyls); 1600 (C=C), 1510, 1450, 1375 (C=N, N=N).	-	66
 (CCXIV)	 (CCXV)	4.39τ (C_2-H_2), 0.95, 0.85 (methyls); 1600 (C=C), 1510, 1450, 1390 (C=N, N=N).	-	66

Table - 1 (Contd.)

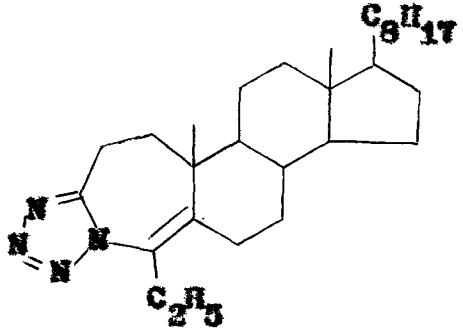
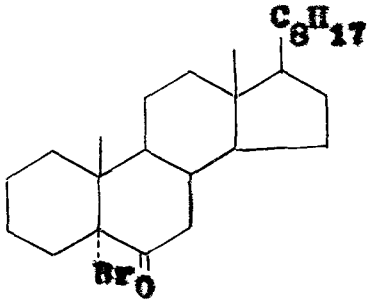
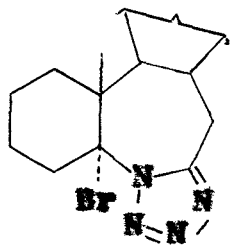
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm (log ϵ)	Ref.
(CCXIV)	 (CCXVI)	2.83m (C_2-H_2), 0.9, 0.8 (methyls); 1630 (C=C), 1530, 1450, 1370 (C=N, N=N).	-	66
 (XXXIV)	 (CCXVII)	3.4d ($C_{7\alpha}$-H; J=15 Hz), 0.9s (C_{10}-Me), 0.71s (C_{13}-Me), 0.83, 0.80 (methyls); 1537 (C=N), 1470, 1370 (N=N), 700 (C-Br).	-	67

Table - 1 (Contd.)

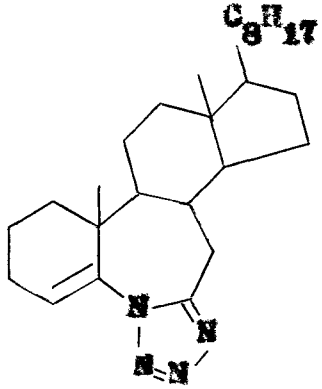
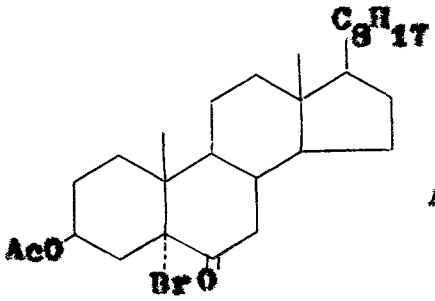
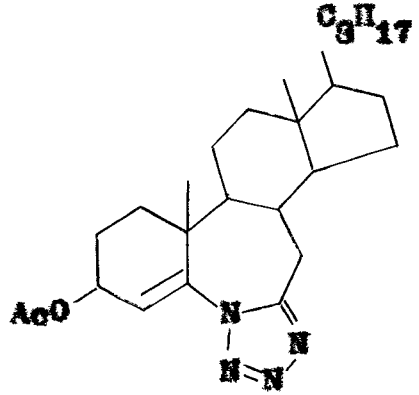
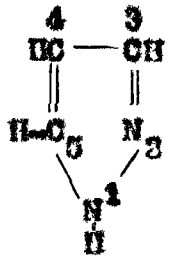
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm ($log_{10}\epsilon$)	Ref.
(XXXIV)	 (CCXVIII)	6.06t (C_6-H), 3.35d (C_{7a}-H; J=15 Hz), 0.92s (C_{10}-Me), 0.45 (C_{13}-Me), 0.63, 0.81 (methyls); 1630 (C=C), 1520 (C=N), 1465, 1395 (N=N).	-	67
(XXXV)	 (CCXIX)	5.3br (C_3-H, $W_{\frac{1}{2}}$ = 16 Hz), 3.4d (C_{7a}-H; J=15 Hz), 2.03s (CH_3-COO), 0.93 (C_{10}-Me), 0.66 (C_{13}-Me), 0.83, 0.76 (methyls); 1725 (CH_3-COO), 1520 (C=N), 1435, 1360 (N=N).	-	67

Table - 1 (Contd.)

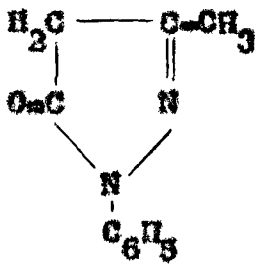
Starting ketone(s)	Product(s)	N.M.R.(δ) and I.R.(cm^{-1})	U.V. nm (log ∈)	Ref.
(XXXV)	 (CCXX)	6.1d (C_4-H; J=3 Hz), 5.33br (C_3-αH; $W\frac{1}{2}$ = 12 Hz), 3.4br,d (C_{7a}-H; J=15 Hz), 2.11s (CH_3-COO), 0.9 (C_{10}-Me), 0.7 (C_{13}-Me), 0.8, 0.75 (methyls); 1730 (CH_3COO), 1643 (C=C), 1510 (C=N), 1460, 1370 (N=N).	-	67

Pyrazole and Pyrazoline Derivatives

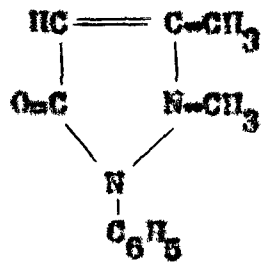
The pyrazole ring system, (CCXXI), consists of a doubly unsaturated five membered ring containing two adjacent nitrogen atoms. Knorr[68,69] first synthesized a compound containing this system in 1883 by the reaction of ethyl acetoacetate with phenyl hydrazine which yielded 1-phenyl-3-methyl-5-pyrazolone (CCXXII). His interest in quinine led to test of the antifebrile action of this and related compounds which resulted in the discovery of antipyrine,[70] (CCXXIII), an important febrifuge.



(CCXXI)



(CCXXII)



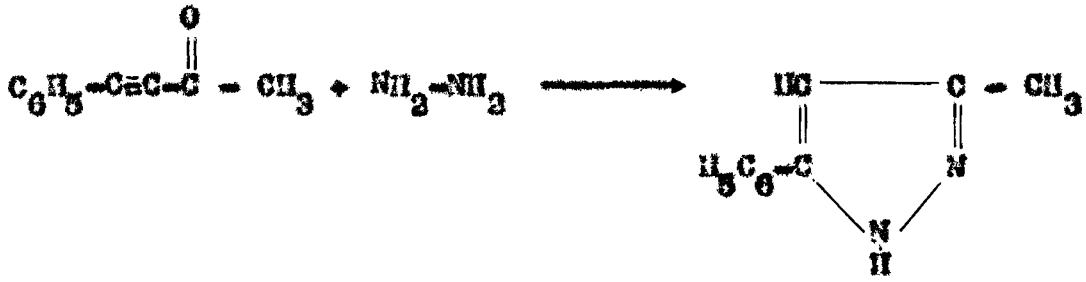
(CCXXIII)

Knorr[71] introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon by nitrogen. He synthesized many members of this class and systematically investigated their properties. Special attention was given to 1-phenylpyrazoles because phenylhydrazine was the most readily available hydrazine and these continue to be the most carefully investigated derivatives. Since many

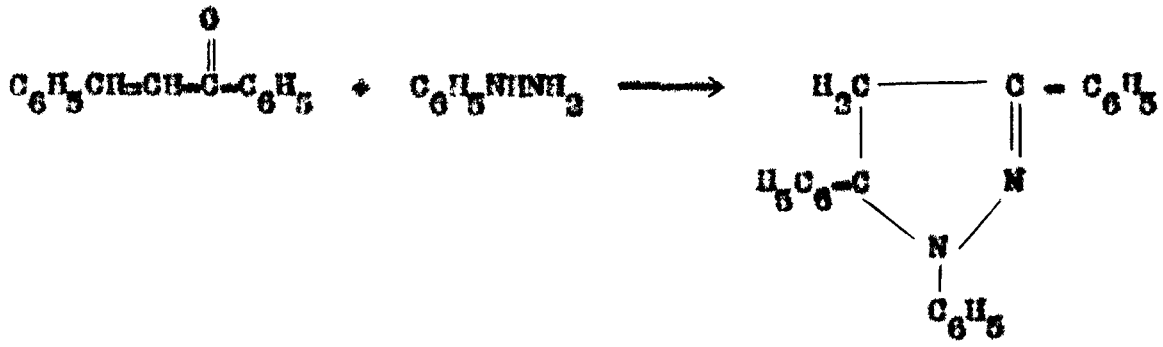
drugs and dyes contain the pyrazole nucleus, the class has been widely studied and the field continues to be active today even though antipyrine and related medicinal compounds are no longer in common use.

The compounds containing this ring system can be synthesized by three general methods:

1. <u>The reaction of hydrazines with α , β -unsaturated carbonyl compounds</u>

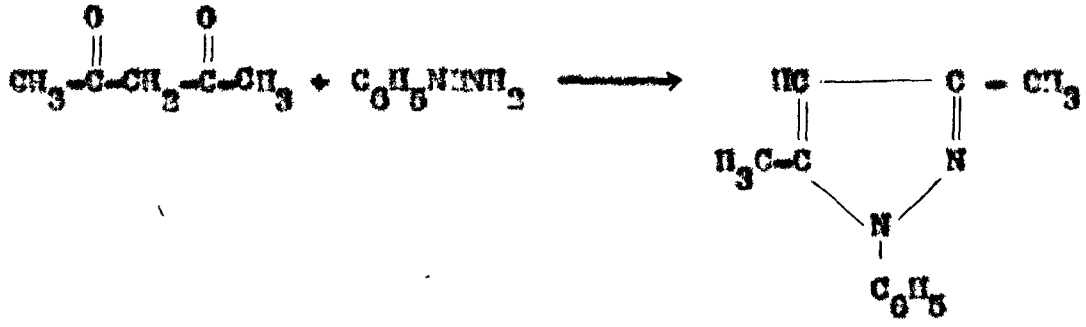


(CCXXIV)



(CCXXV)

2. **The reaction of phenyl hydrazine or its derivatives such as aryl or alkyl hydrazines, semicarbazide or aminoguanidine with 1,3-dicarbonyl compounds**



(CCXXVI)

The synthesis of pyrazolones from β-ketoesters is analogous to the preparation of pyrazole (CCXXVI).

3. **The reaction of aliphatic diazocompounds such as diazo methane or diazo aceticester with acetylenes or olefins**

It has been observed by different group of workers[72-79] that the synthesis of pyrazoles by the reaction of α,β-unsaturated acetylenic carbonyl compounds with hydrazine and its derivatives is less common than the corresponding pyrazoline synthesis from α,β-ethylenic carbonyl compounds. The synthesis

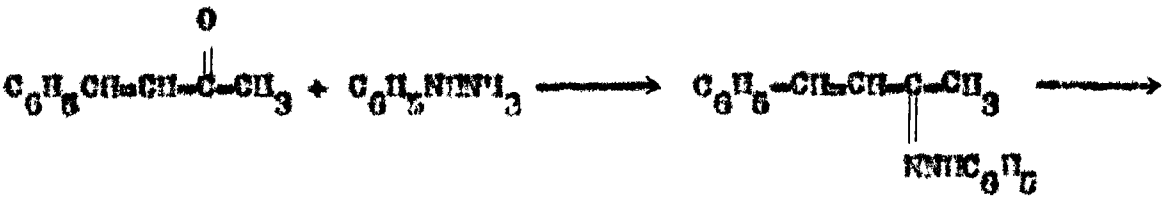
of the acetylenic ketones by oxidation of the corresponding carbinols[72] has made these more accessible, but 1,3-dicarbonyl compounds that yield the same pyrazoles are usually obtained more easily. The pyrazole synthesis is generally more facile when hydrazine is used,[73-76] and a hydrazone is seldom isolated;[77] difficulties are encountered occasionally.[78,79]

The synthesis of pyrazole, it might be assumed, involves the formation of a hydrazone as intermediate and thus the structure of the 1,3- or 1,5-disubstituted pyrazole is determined. This need not be true, because the addition of amines to the triple bond of α,β-acetylenic carbonyl compounds is well known,[80,81] and addition of the hydrazine in a similar manner may be the first step in the reaction.[78]

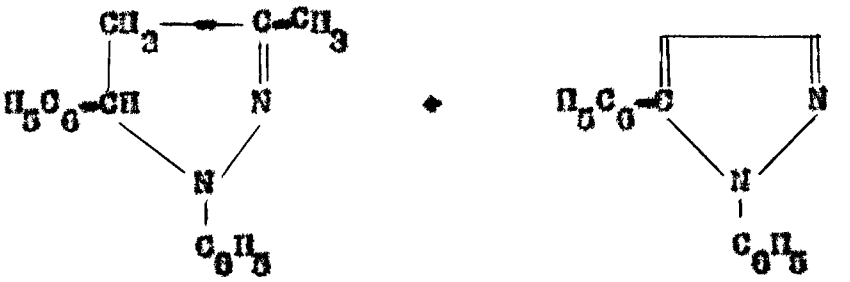
The presence of electron-releasing group such as hydroxyl, alkoxyl, and amino on either phenyl group of benzal acetophenone makes the phenylhydrazone more labile, and it can seldom be isolated;[82-85] electron-withdrawing groups such as nitro and halogen stabilize the intermediate.[85-87]

It is expected that the reaction of an α,β-unsaturated carbonyl compound with phenylhydrazine or other substituted hydrazines would proceed through hydrazone formation and ring closure in a straight forward way to give a pyrazoline or pyrazole. This has been shown to be the course of the reaction

with benzal acetone[88] phenylhydrazone (CCXXVII) to yield the pyrazoline (CCXXVIII) and pyrazole (CCXXIX).



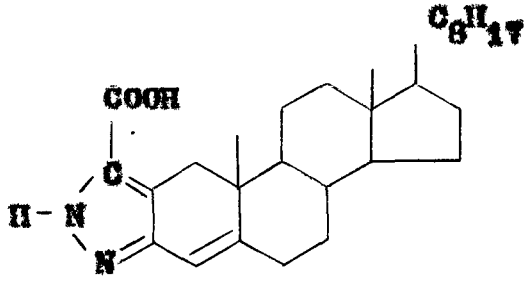
(CCXXVII)



(CCXXVIII) (CCXXIX)

Steroidal Pyrazoles

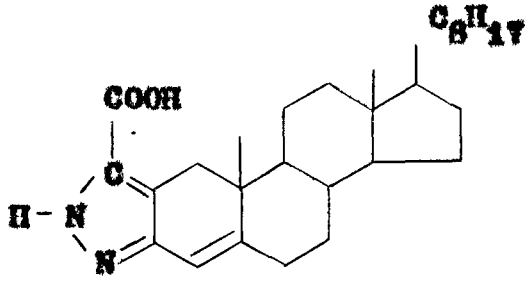
Survey of the literature reveals that very little mention, till 1930s, had been made about the synthesis of steroidal pyrazole derivatives. Probably the first steroidal pyrazole was reported by Ruzicka et al.[89] in 1938. Only a single derivative, cholest-4-eno [3,2-c] pyrazole-5'-carboxylic acid (CCXXX), was mentioned.



(CCXXX)

After a considerable span of time, much attention has been paid by a number of organic chemists towards the synthesis of several pyrazolosteroids. The effect on endocrinological activity produced by the fusion of a pyrazole ring to a steroid nucleus has prompted them to investigate such type of compounds. In the year 1959, Clinton et al,[00] reported several steroidal [3,2-c] pyrazoles constituting a novel series of considerable endocrinological interests. Some of the compounds showed a remarkable separation, or change in pattern, of hormonal activity when compared with the parent steroids.

They reported[00] that treatment of 17α-methylandrostan-17β-ol-3-one (CCXXXI) with ethyl formate and sodium methoxide gave the 2-hydroxymethylene derivative (CCXXXII) which on condensation with hydrazine gave 17β-hydroxy-17α-methylandrostano [3,2-c] pyrazole (CCXXXV). Similar treatment of 2-hydroxy-methylene-17α-methylandrost-4-en-17β-ol-3-one (CCXXXIII) furnished 17β-hydroxy-17α-methylandrost-4-eno [3,2-c] pyrazole



(CCXXX)

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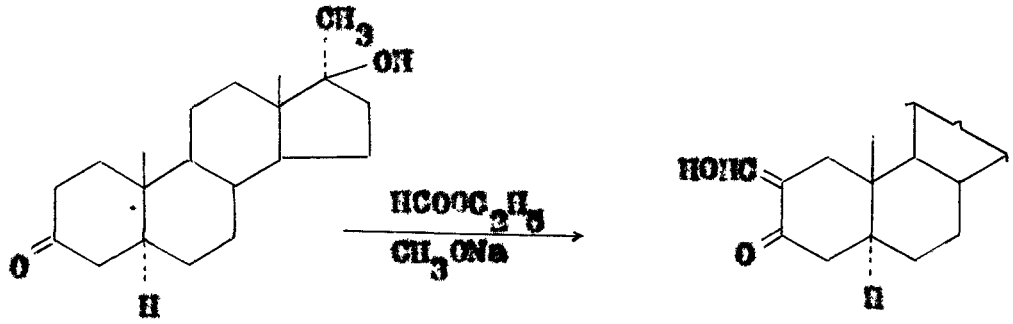
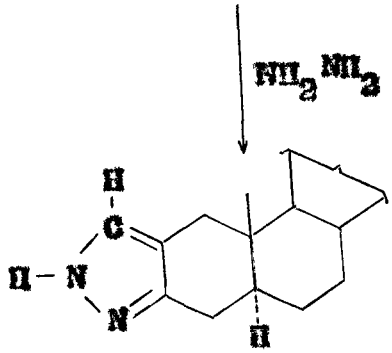
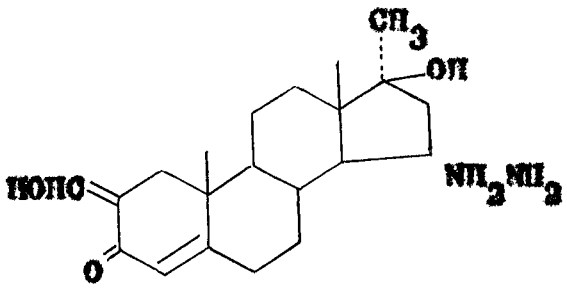
(CCXXXVI). In the same way, the homologous 17β-hydroxy-17α-methylandrosta-4,6-dieno [3,2-c] pyrazole (CCXXXVII) was obtained from (CCXXXIV).



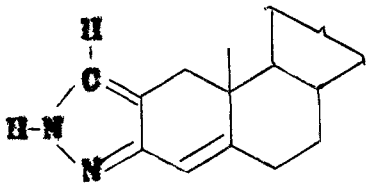
(CCXXXI) (CCXXXII)



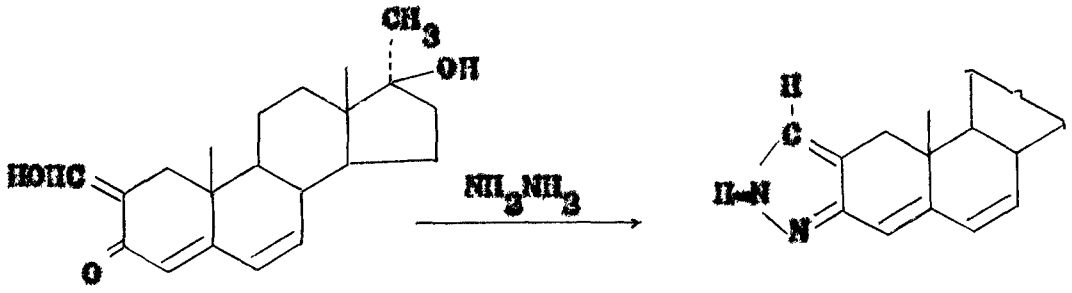
(CCXXXV)



(CCXXXIII)



(CCXXXVI)



(CCXXXIV) (CCXXXVII)

Clinton et al.[90] summarized qualitatively the hormonal patterns observed for a series of 17α-methyl-17β-hydroxyandrostane derivatives (CCXXXV-CCXXXVII) when tested in rats as shown in the table 2 given below.

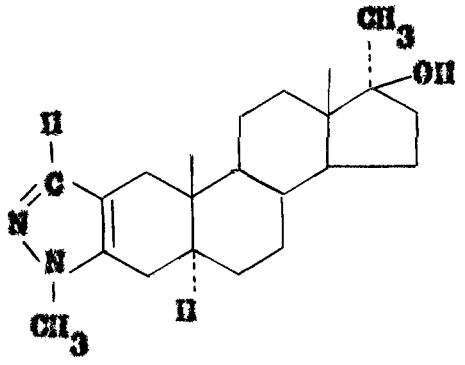
Table - 2

Compounds	Estrogenic (Vaginal Cornification)	Androgenic (Ventral prostate growth)	Myotrophic (Levator and growth)	Anabolic (Nitrogen retention)
(CCXXXV)	-	+	+	+
(CCXXXVI)	+	+	+	-
(CCXXXVII)	+	-	-	?
N-Acetyl (CCXXXV)	+	+	+	+
N-Acetyl (CCXXXVI)	+	+	+	?

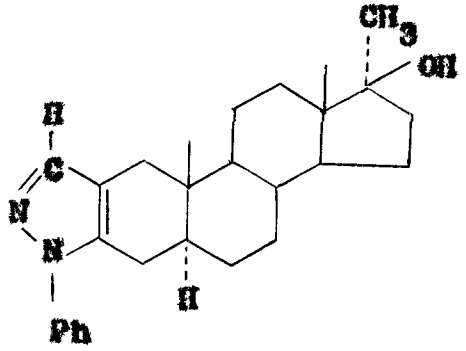
The unusual activity observed by the above mentioned pyrazolosteroids led to the preparation of compounds related to the progestational and cortical hormones, as well as to the fusion of steroids with other heterocyclic rings. Some of the simple 2-hydroxymethylene-3-keto-17α-alkyl androstanes and their $\triangle^4$-analogues had a fair to good degree of oral anabolic activity. In all cases, however, the anabolic activities of the 2-hydroxymethylene-3-keto progenitors were less interesting than those of their steroidal [3,2-c] pyrazole derivatives. It is pertinent to point out that one of these compounds, viz., 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one (CCXXXII) had shown oral anabolic activity in humans.[91]

With the view of synthesizing anabolic agents, efforts were continued and consequently in 1961, Glinton and co-workers[92] reported several steroidal [3,2-c] pyrazoles. Attempts had been made to vary endocrine activity patterns by means of alteration within or substitution on, the steroid nucleus. With this concept, they prepared steroidal [3,2-c] pyrazoles; 17β-hydroxy-17α-methylandrostano [3,2-c]-2'-methyl pyrazole (CCXXXVIII), 17β-hydroxy-17α-methylandrostano [3,2-c]-2'-phenyl pyrazole (CCXXXIX), 17β-acetoxy-17α-methylandrostano [3,2-c] pyrazole (CCXL), 17β-hydroxyandrost-4-eno [3,2-c] pyrazole (CCXLI), 17-ketoandrost-4-eno [3,2-c] pyrazole (CCXLII), 17β-hydroxy-17α-methyl-19-norandrost-4-eno [3,2-c]

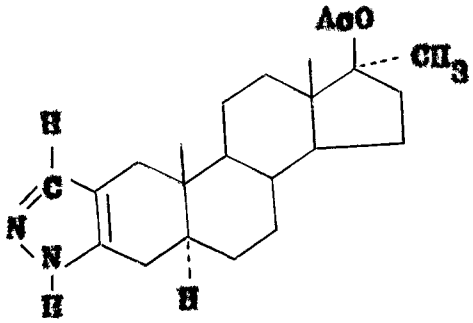
pyrazole (CCXLIII) and 17β-hydroxy-, 17α-methylandrosta-4,6-dieno [3,2-c] pyrazole (CCXXXVII) from their corresponding 2-hydroxymethylene-3-ketoandrostanes.



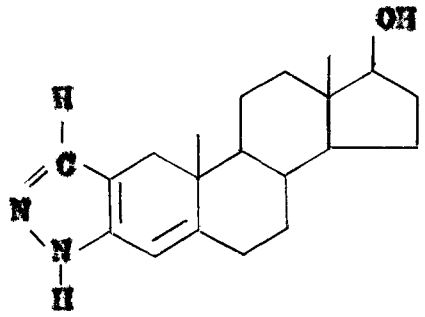
(CCXXXVIII)



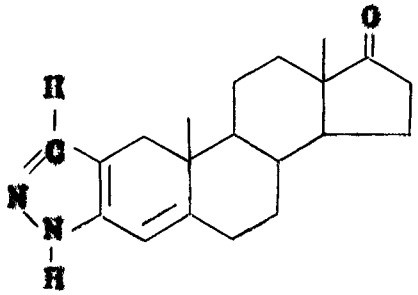
(CCXXXIX)



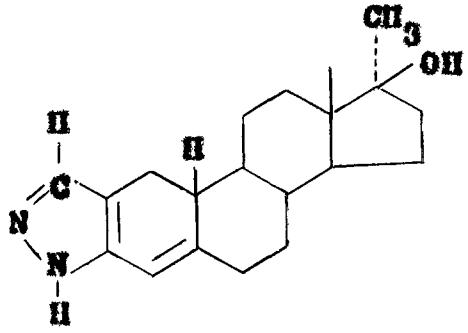
(CCXL)



(CCXLI)

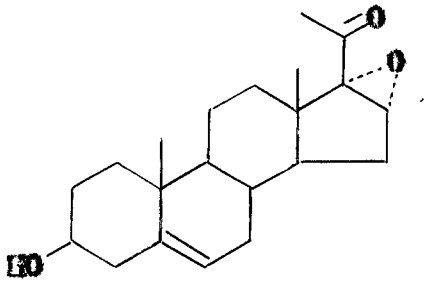


(CCXLII)

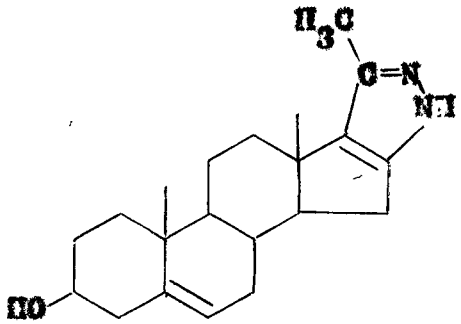


(CCXLIII)

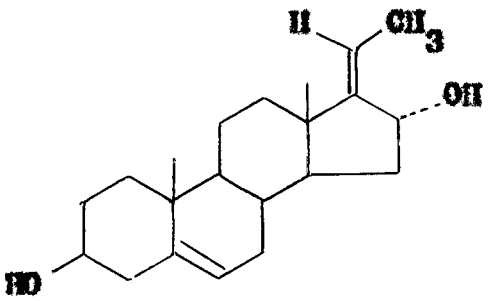
Dorn and Dodson,[93] in 1964, carried out the hydrazine reduction of 16α,17-epoxy-pregnenolone (CCXLIV) and obtained 3β-hydroxyandrost-5-eno [16,17-c]-5'-methyl pyrazole (CCXLV) along with the two isomeric allylic alcohols, 5,17(20)-(cis)-pregnadiene-3β,16α-diol (CCXLVI) and 5,17(20)-(trans)-pregnadiene-3β,16α-diol (CCXLVII).



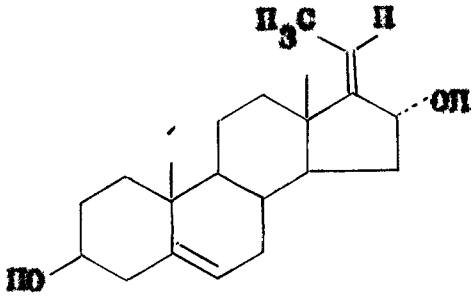
(CCXLIV)



(CCXLV)



(CCXLVI)



(CCXLVII)

The steroidal pyrazole (CCXLV) was shown[93] to be readily identified by its spectral analysis, (i.r. and U.v.) and by analogy with previous reactions of α ,β-epoxy ketones with hydrazine.[94]

In 1964, Hirschmann and co-workers[95] also reported several [3,2-c] pyrazoles related to cortisol, 16α-methylcortisol, and 4,5α-dihydrocortisol. It was found that the N-substituted and N-alkylated pyrazoles displayed biological activity of the same order of magnitude as the parent steroids. Even more surprising was the observation that the 2'-phenyl- and especially the 2'-p-fluorophenyl derivatives were infact the most powerful activity-enhancing functions so far disclosed in the anti-inflammatory area. These results, moreover, strongly suggest that the pyrazoles are active as such and not as result of a biological regeneration of the steroidal 3-keto group as observed by others.[90,96-98]

The cortical side chain of (CCXLVIII) was protected by formation of the bismethylenedioxy (BMD) derivative (CCXLIX) for the synthesis of pyrazoles related to 16α-methylcortisol. The compound (CCXLIX) was allowed to react with ethyl formate in benzene in the presence of sodium hydride to give the 3-hydroxymethylene derivative (CCL). The compound (CCL) was actually subjected to condensation with hydrazine, phenyl hydrazine, N-substituted and N-alkylated hydrazines to yield

the [3,2-c] pyrazoles (CCLII-CCLXIII) which is summarised in Charts 1 and 3.

Chart - 1

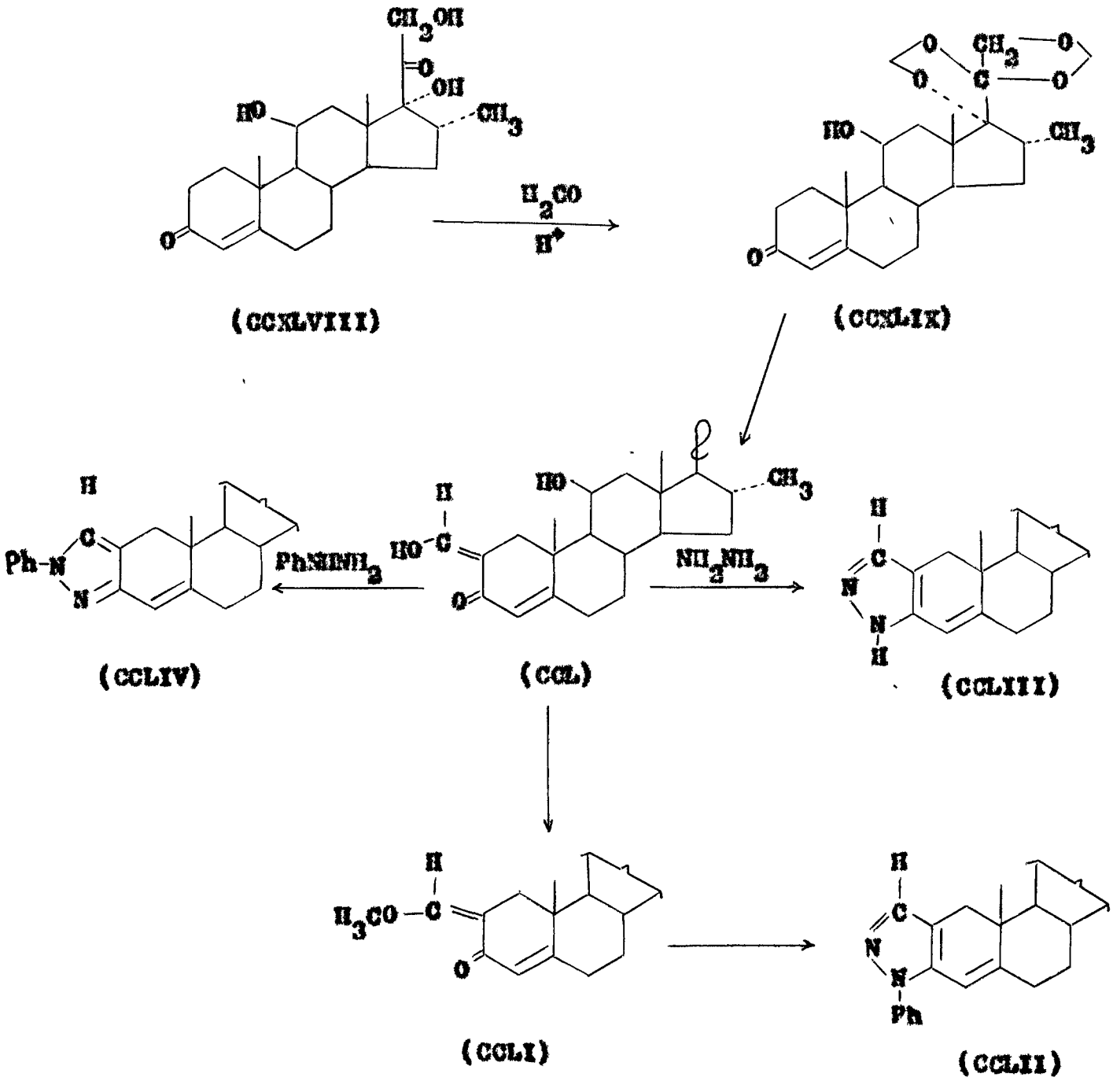
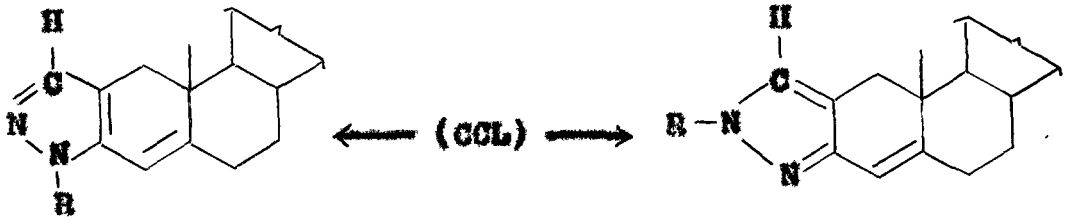
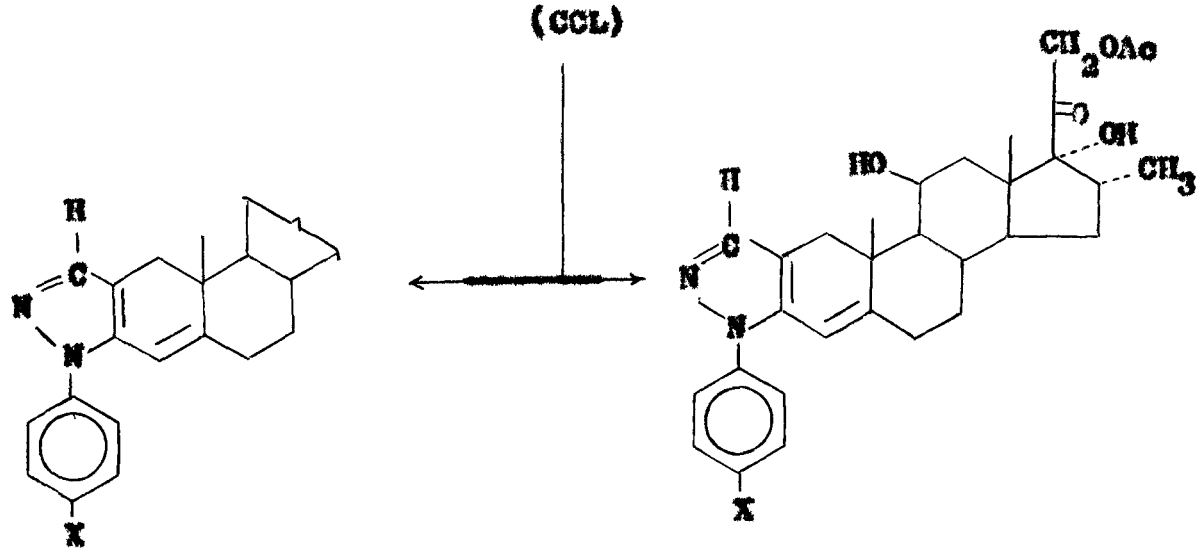


Chart - 2



(CCLV) R, CH_3
(CCLVII) R, $-CH_2CH_2OH$

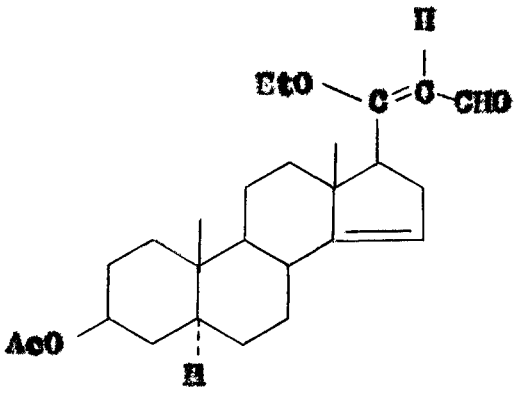
(CCLVI) R, CH_3
(CCLVIII) R, $-CH_2CH_2OH$



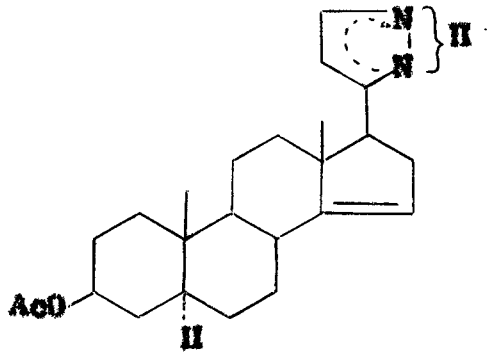
(CCLIX) X, F
(CCLX) X, Cl
(CCLXI) X, H

(CCLXII) X, H
(CCLXIII) X, F

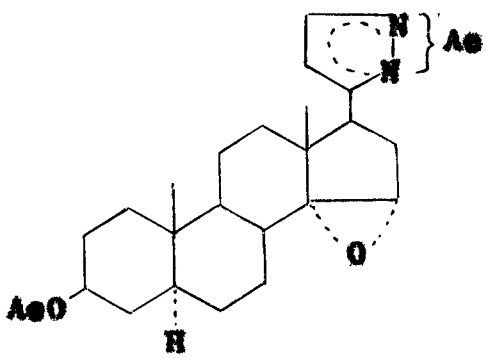
The reaction of 20-ethoxy-21-formyl-17β-pregna-14,20-diene (CCLXIV) with hydroxylamine and hydrazine hydrate afforded[99] 17β-(3-pyrazolyl)-3β-acetoxy-5α-androst-14-ene (CCLXV) which was subjected to N-acetylation followed by epoxidation with monoperphthalic acid to give the α-epoxy product (CCLXVI). The compound (CCLXVI) on alkaline hydrolysis, resulted in the formation of the desired 17β-(3-pyrazolyl)-14α,15α-epoxyandrostene (CCLXVII).



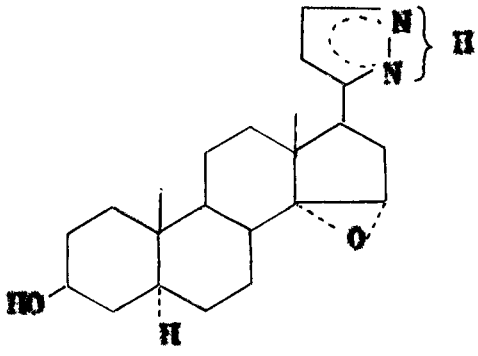
(CCLXIV)



(CCLXV)

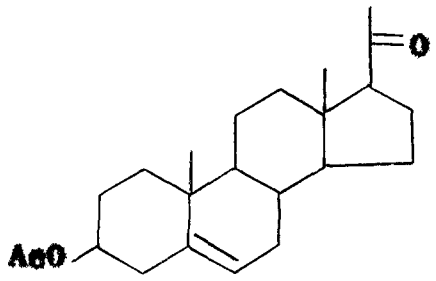


(CCLXVI)

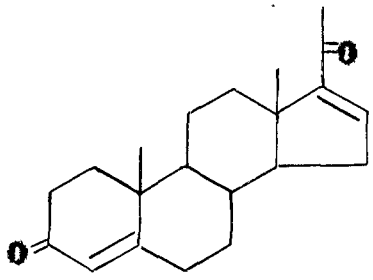


(CCLXVII)

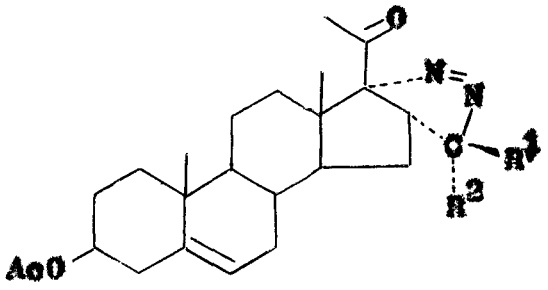
The reaction of a series of aliphatic diazo compounds with Δ^{16}-20-oxo-steroids has been performed by Bladon et al.[100,101] It has been shown that diazo compounds (diazopropene, diazopropyne, 3-diazopropane, and diazo-cyclopropane) allowed to react with 3β-acetoxypregna-5,16-dien-20-one (CCLXVIII) and pregna-4,16-diene-3,20-dione (CCLXIX), furnished the [17α, 16α-C] pyrazolines (CCLXXa-c) and (CCLXXIa-d), respectively.



(CCLXVIII)

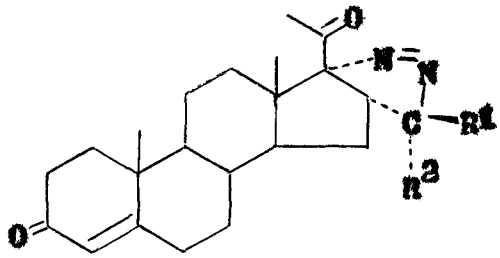


(CCLXIX)



(CCLXX)

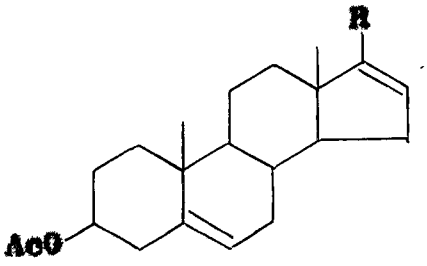
	R_1	R_2
a,	$-CH=CH_2$	H
b,	H	$-CH=CH_2$
c,	$-C\equiv CH$	H
d,	Me	Me
e,	$-CH_2CH_3-$	$-CH_2-CH_3-$



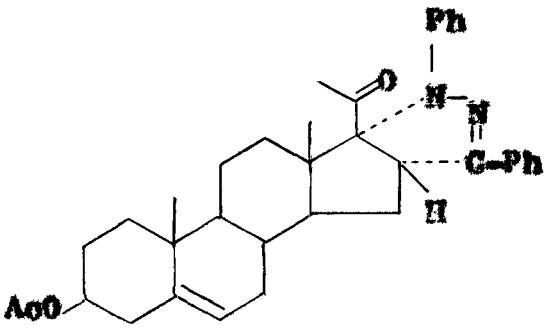
(CCLXXI)

	R_1	R_2
a,	$-CH=CH_2$	H
b,	$-C\equiv CH$	H
c,	Me	Me
d,	$-CH_2-CH_3-$	$-CH_2CH_2$
e,	H	$-C\equiv CH$

Recently Green et al.[103] reported the synthesis of a number of steroidal pyrazoles and pyrazolines in the androstane series related to those obtained by Bladon and his co-workers.[100,101] The addition of triethylamine to a mixture of the compound (CCLXVIII) and benzoyl chloride phenylhydrazone led to the 65% yield of 3β-acetoxypregna-5-en-20-one [16α,17α-d]-1',3'-diphenyl-3'-pyrazoline (CCLXXIII) as predicted.

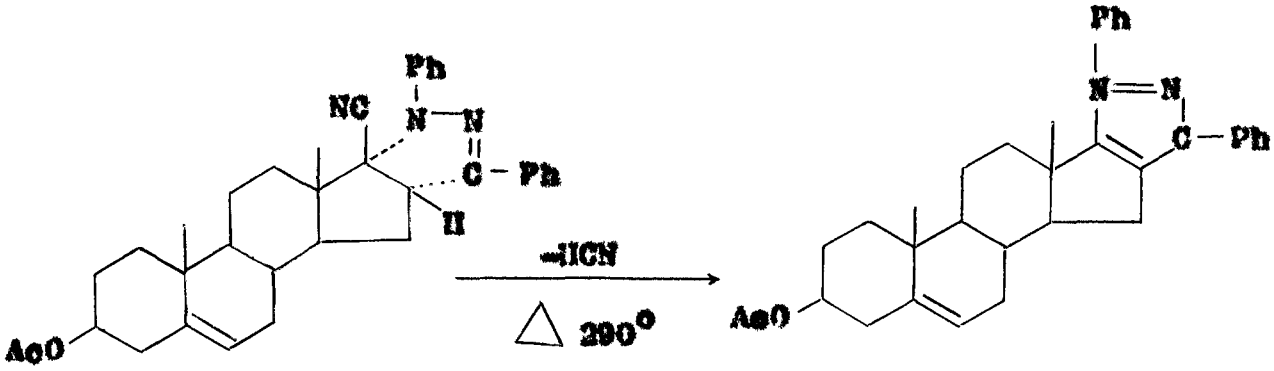


(CCLXVIII) R, $-COCH_3$
(CCLXXII) R, CN



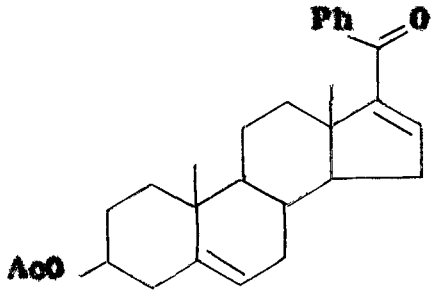
(CCLXXIII)

Similarly, the addition of diphenyl nitrilimine to 3β-acetoxy-17-cyanoandrosta-5,16-diene (CCLXXII) took place in the same regiochemical sense to yield 3β-acetoxy-17β-cyanoandrost-5-eno [16α,17α-d]-1',3'-diphenyl-2'-pyrazoline (CCLXXIV). The pyrolysis of (CCLXXIV) at 290° resulted in the formation of 3β-acetoxyandrost-5-eno [16,17-d]-diphenyl pyrazole (CCLXXV).

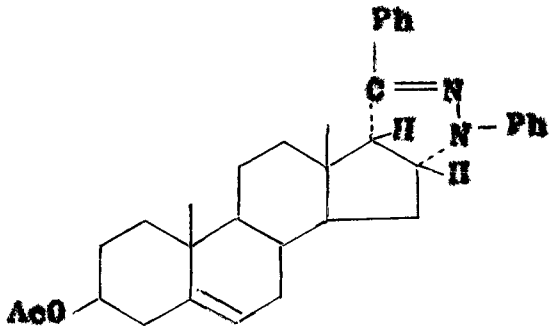


(CCLXXIV) (CCLXXV)

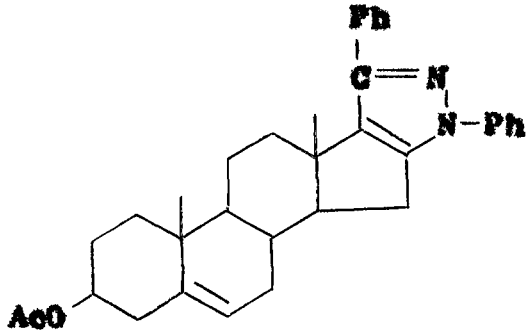
To confirm the regiochemistry of pyrazole (CCLXXV), its regioisomer was prepared by converting the 17-substituted-16,17-androstene (CCLXXVI) to its phenylhydrazone followed by cyclization with ethanolic hydrochloric acid to the diphenyl-pyrazoline (CCLXXVII), which was dehydrogenated with dichloro-dicyanobenzoquinone to yield the desired 3β-acetoxyandrost-5-eno [17,16-d]-1',3'-diphenyl pyrazole (CCLXXVIII). The pyrazole (CCLXXVIII) differed markedly in m.p., i.r., n.m.r., u.v. and o.r.d. with that of (CCLXXV). The compound (CCLXXVIII) after pyrolysis afforded (CCLXXIX).



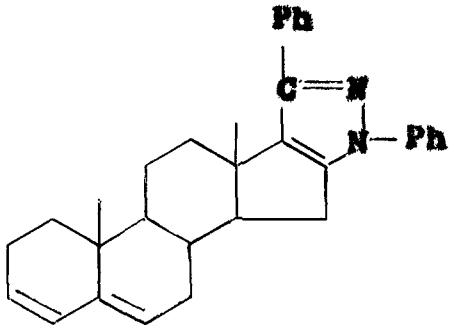
(CCLXXVI)



(CCLXXVII)

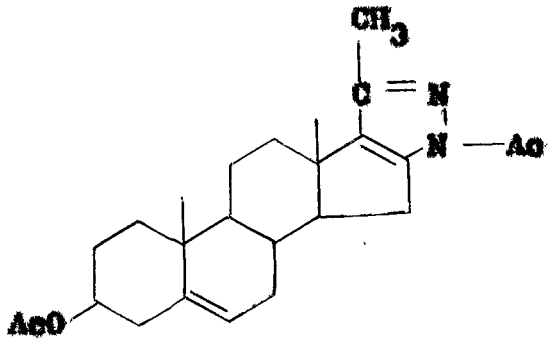


(CCLXXVIII)



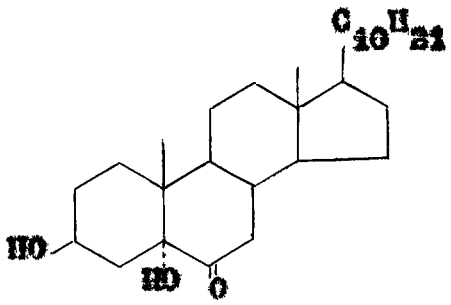
(CCLXXIX)

In the year 1980, Kamarnitskii et al.[103] have observed that the condensation of the steroidal ketone (CCLXVIII) with substituted hydrazines afforded the N-substituted pyrazole (CCLXXX).

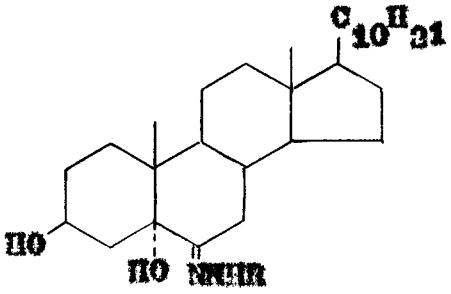


(CCLXXX)

Habib et al.[104] synthesized several steroidal hydrazones in the stigmastane series. They claimed that 6-aryl hydrazono-, aroyl hydrazono- and thiosemicarbazono-5α-stigmastane-3α,5α-diol to possess potential antilipemic activity. The stigmastanone hydrazones (CCLXXXIIa-d) were prepared from the condensation of 3β,5α-dihydroxy stigmastan-6-one (CCLXXXI) with substituted hydrazine. However, the cyclization of those hydrazones leading to the formation of corresponding pyrazoles has not yet been reported.



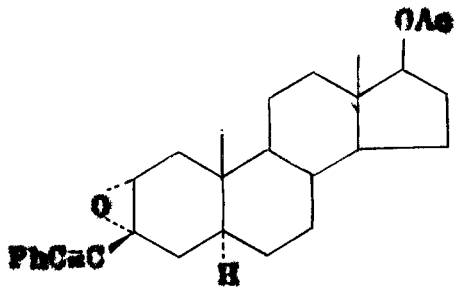
(CCLXXXI)



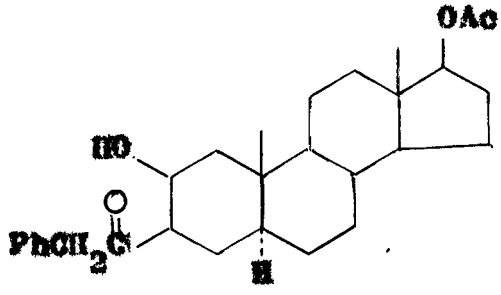
(CCLXXXII)

a, R, Me-C_6H_4
b, R, Cl-C_6H_4
c, R, HO_2C-C_6H_4
d, R, Bz

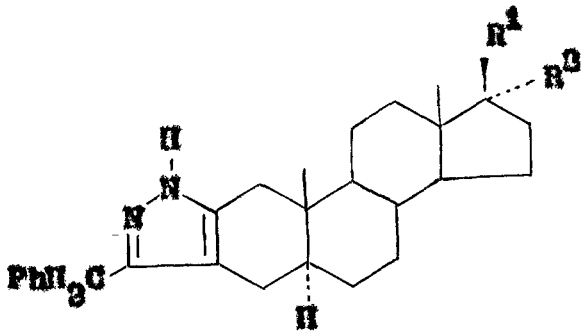
Berbalk and his co-workers[105] in 1963 reported that the epoxyandrostane (CCLXXXIII) underwent formolysis to give phenyl acetyl androstane (CCLXXXIV). Cyclocondensation of (CCLXXXIV) with hydrazine afforded androsteno-pyrazoles (CCLXXXV-CCLXXXVII).



(CCLXXXIII)



(CCLXXXIV)

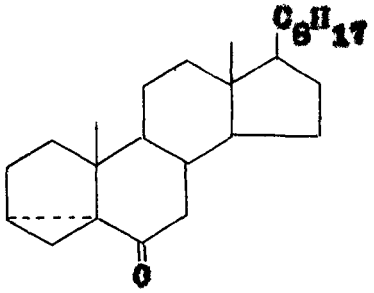


	R_1	R_3
(CCLXXXV)	OAc	H
(CCLXXXVI)	OH	H
(CCLXXXVII)	R R' = O	

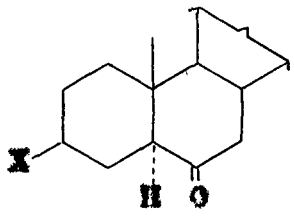
DISCUSSION

Oxasteroids

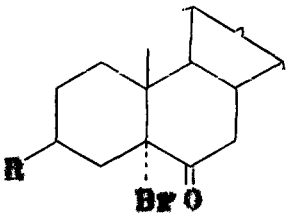
The Baeyer-Villiger oxidation of steroidal ketones, both saturated as well as α,β-unsaturated ones, has been extensively studied. In the preceding years, a number of communications from this laboratory described the work on the synthesis of oxasteroids. These reactions provided a variety of interesting rearranged products and their formation depended to a large extent on the peracid employed, the catalyst used and the reaction period. The substrates on which previous studies centred were 3α-5-cyclo-5α-cholestan-6-one (XVII), its 3β-haloderivatives-(XVIII-XX)[9], 5-bromo-5α-cholestan-6-one (XXIV), its 3β-acetoxy analogue (XXV)[13], 4α-acetoxycholest-5-en-3-one (XXVII),[11] cholest-4-en-6-one (LXXX),[33] 3β-acetoxycholest-4-en-6-one (LXXXVI),[34] cholest-4-ene-3,6-dione (XCII),[30] cholest-5-en-7-one (CII), its 3β-acetoxy analogue (XCVIII)[37] and 3β-acetoxystigmast-4-en-6-one (CXIX).[42]



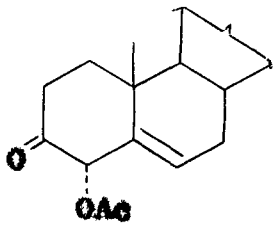
(XVII)



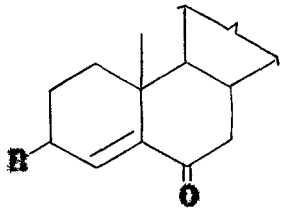
(XVIII) X, Cl
(XIX) X, Br
(XX) X, I



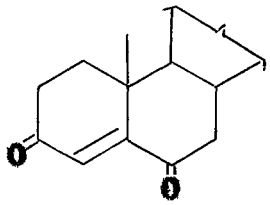
(XXXIV) R, H
(XXXV) R, OAc



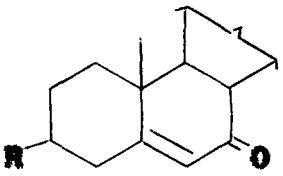
(XXVII)



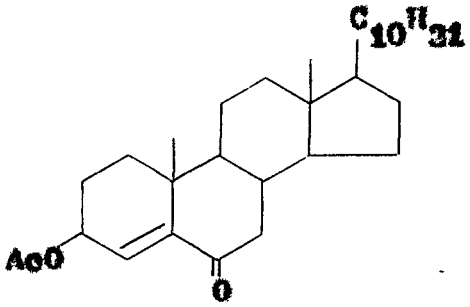
(LXXX) R, H
(LXXXVI) R, OAc



(LXXI)

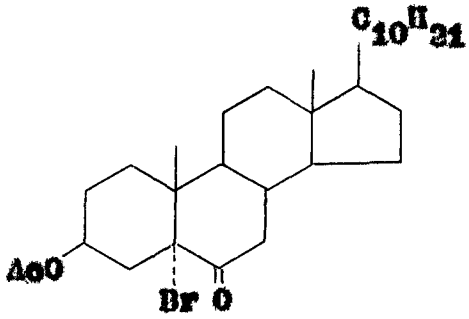


(CII) R, H
(XCVIII) R, OAc

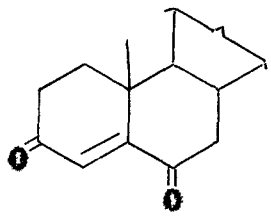


(CXIX)

With a view of extending the work in the stigmastene series, we carried out the Baeyer-Villiger oxidation of 3β-acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII) and stigmast-4-ene-3,6-dione (CCLXXXIX) with perbenzoic acid using p-toluenesulphonic acid as catalyst.



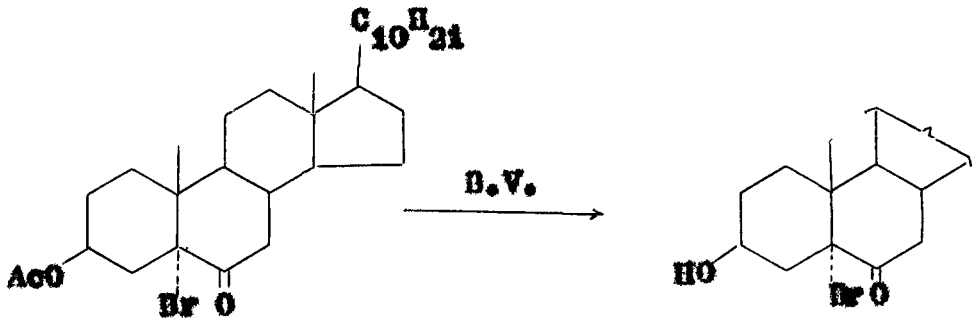
(CCLXXXVIII)



(CCLXXXIX)

<u>Baeyer-Villiger oxidation of 3β-acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII)</u>

The Baeyer-Villiger oxidation of 3β-acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII) with 2 mole equivalent of perbenzoic acid using p-toluenesulphonic acid as catalyst, was performed in order to see the effect of 5α-bromine on the course of the reaction. After usual work up and column chromatography the reaction mixture provided two compounds, m.ps. 140° and 320°.



(CCLXXXVIII) (CCXC)

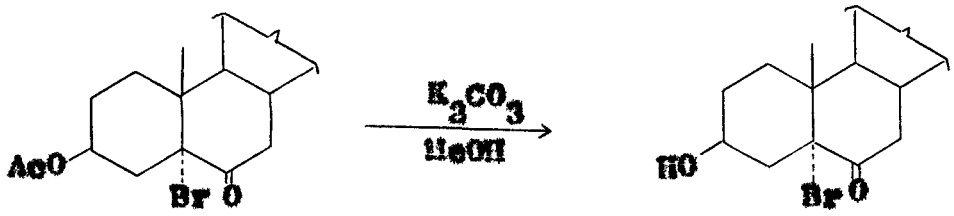
(CCXCI) (CCXCII)

<u>Characterization of the compound, m.p. 140° as 3β-hydroxy-5α-bromostigmastan-6-one (CCXC)</u>

The compound m.p. 140° correctly analysed for $C_{29}H_{49}O_3Br$ (positive Beilstein test), showed bands in its i.r. spectrum at 3330 cm^{-1} which can be assigned to its hydroxyl function. The other bands were observed at 1700 and 720 cm^{-1}. The bands at 1700 and 720 cm^{-1} can be assigned to carbonyl function and C-Br stretching, respectively. The n.m.r. spectrum of the compound exhibited signals at δ 3.3 br (1 proton, C_3-H, axial;

$W_{\frac{1}{2}}$ 17 Hz) and 2.3 br,s (2 protons, C_7-protons). Other signals were obtained at δ0.91, 0.72 and 0.6 (methyl protons). On the basis of the foregoing discussion, the compound m.p. 140° can be characterized as 3β-hydroxy-5α-bromostigmastan-6-one (CCXC), a product of simple hydrolysis of 3β-acetate function of (CCLXXVIII).

The compound (CCXC) was also obtained when (CCLXXVIII) was hydrolysed under basic conditions. Its m.m.p. and t.l.c. were found to be identical with the authentic sample (CCXC).



(CCLXXVIII) (CCXC)

Characterisation of the compound m.p. 320° as 6-oxa-D-homo-5α-bromostigmastane-3,7-dione (CCXCI)

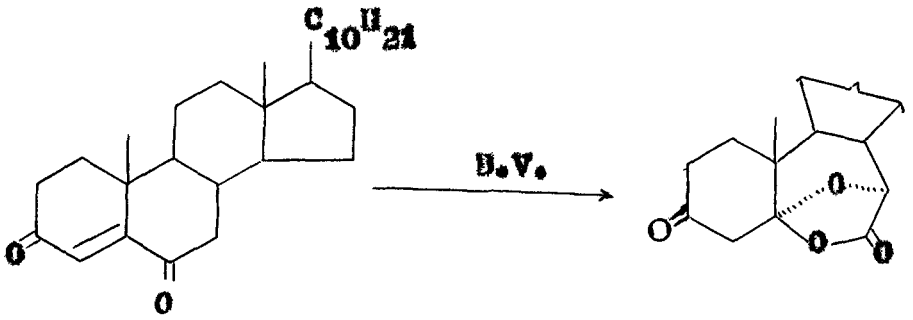
The compound, m.p. 320° analysed for $C_{29}H_{47}O_3Br$. It showed positive Beilstein test. The compound, m.p. 320° gave bands in its i.r. spectrum at 1715, 1700 and 720 cm^{-1}. The bands at 1700 and 1715 cm^{-1} could be attributed to the two carbonyl groups, one of which could be ϵ-lactone carbonyl

function. The compound did not show acetate or hydroxyl function. The band appearing at 720 cm^{-1} can be assigned to C-Br stretching. Its elemental analysis reveals that it has no oxygen less than the substrate (CCLXXXVIII). The possibility for the structure (CCXCII) may also be expected in the light of earlier observations[13] in the cholestane series where the Baeyer-Villiger oxidation of 5α-bromo-6-keto steroids afforded 7-oxa isomer as one of its reaction products. A clear distinction can be made among its various possible structures on the basis of its n.m.r. spectrum. Its n.m.r. spectrum showed broadened signal at δ 3.35 integrating for six protons. The appearance of signal for six protons in close vicinity in its n.m.r. spectrum requires some additional comments. The previously reported[13] 8-ring ϵ -lactones having C_5-αH orientation, showed a broadened singlet and a doublet of C_{7a}-pseudo equatorial (β) and C_{7a}-pseudo axial (α) protons, respectively. But the same splitting nature of C_{7a}-protons was not seen in this case. It was thought that the presence of a bromine atom at C_5 affects the C_4 protons and for this reason signals for all the protons of C_3, C_4 and C_7 appeared as a broad multiplet at δ 3.35. The structure (CCXCII) is discarded in the light of earlier report[13] in which signals for C_{7a} protons for such structure have appeared at much lower field. It is also believed that the acetate function in (CCLXXXVIII) was hydrolysed and then oxidised to ketone by perbenzoic acid during the course

of the reaction. Other signals in n.m.r. spectrum were seen at δ 0.9, 0.81 and 0.75 (methyl protons). On the basis of the above discussions, the compound, m.p. 230° may be characterized as 6-oxa-B-homo-5α-bromostigmastane-3,7-dione (CCXCI).

Reaction of stigmast-4-ene-3,6-dione (CCLXXXIX) with perbenzoic acid

Oxidation of stigmast-4-ene-3,6-dione (CCLXXXIX) with 3.3 mole of perbenzoic acid (p-toluenesulphonic acid monohydrate as catalyst) provided after usual work up and column chromatography three compounds, m.ps. 105°, 206° and an oil, respectively.

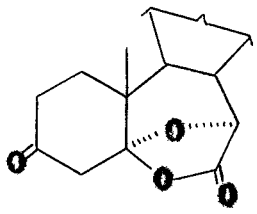


(CCLXXXIX) (CCXCIII)

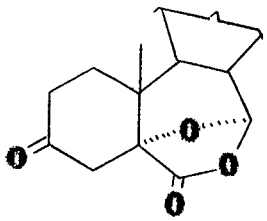
(CCXCIV) (CCXCV)

Characterisation of the compound, m.p. 105° as 5α,7aα-oxido-6-oxa-B-homoetiocholane-3,7-dione (CCXCIII)

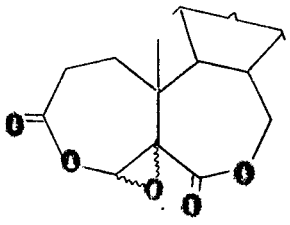
The compound, m.p. 105° analysed for $C_{20}H_{30}O_4$. The molecular composition of the compound reveals that two atoms of oxygen have been added to the substrate (CCLXXIX) during the course of reaction and this leads to several possibilities for its structure (CCXCIII, CCXCVI-CCCI).



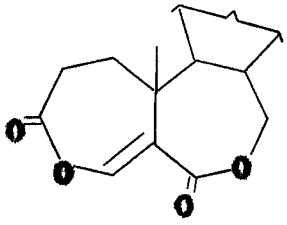
(CCXCIII)



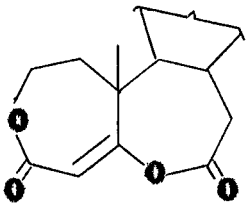
(CCXCVI)



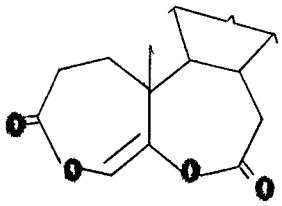
(CCXCVII)



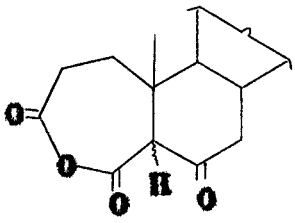
(CCXCVIII)



(CCXCIX)



(CCC)



(CCCI)

The i.r. spectrum gave bands at 1703s, 1720s, 1190m, 1140m and 930s cm^{-1}. The u.v. spectrum was found to be featureless in the region 200-300 nm, thus indicating the absence of an α,β -

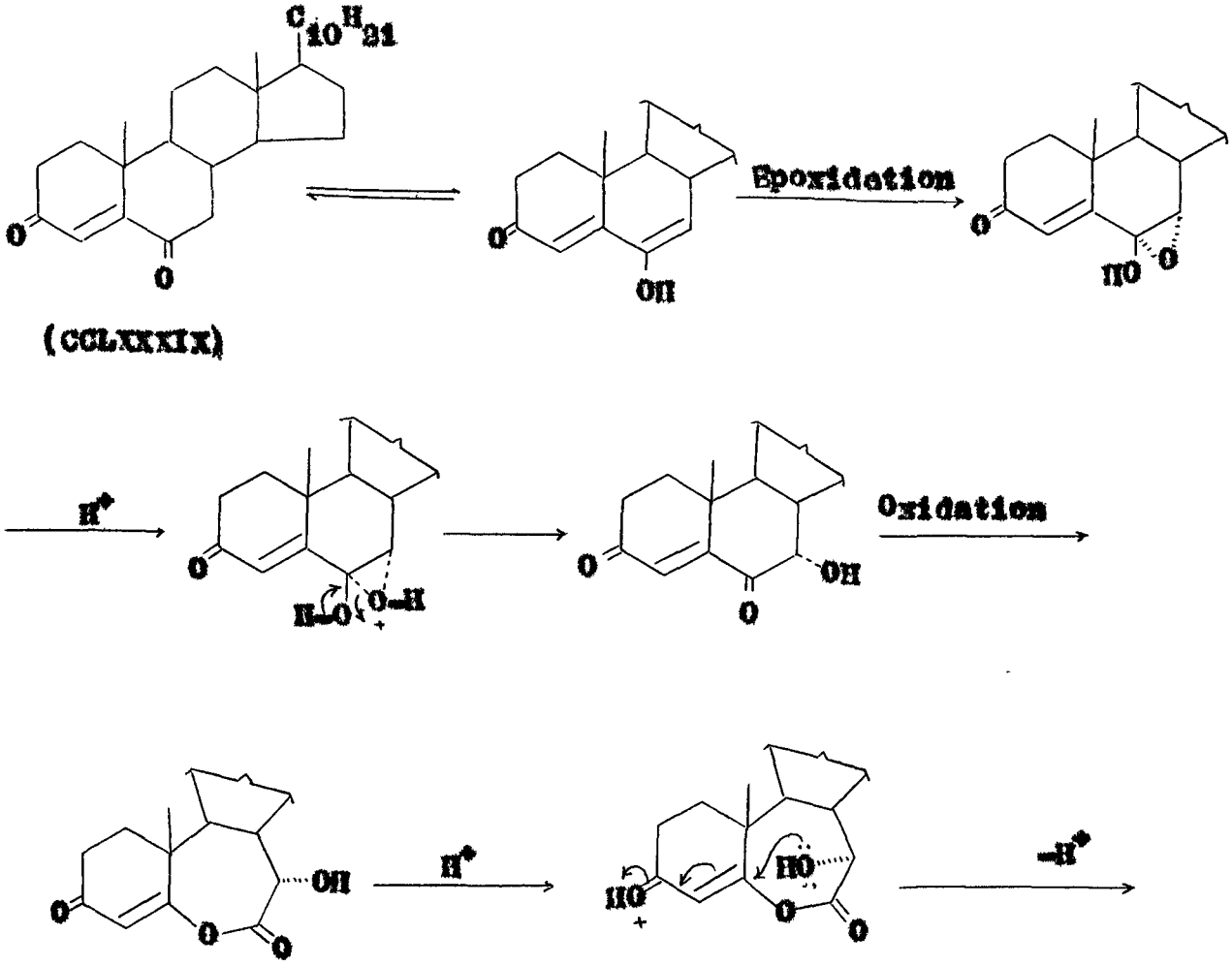
unsaturated carbonyl chromophore in the molecule. The n.m.r. spectrum exhibited signals at δ 5.5s (1H, C7α-H), 3.0d (1H, J 15 Hz; gem coupling) and 2.3d (1H, J 15 Hz; gem coupling). In the light of earlier work,[36,106] the latter two signals are ascribable to the two nonequivalent protons of an isolated methylene group (AB system centred at δ 2.6). Other signals were seen at δ1.01 (C_{10}-CH_3), 0.70 (C_{13}-CH_3), 0.93 and 0.87 (other methyl groups). In addition to (CCXCIII), the possible structures such as (CCXCVI-CCCI) are also compatible with the composition $C_{29}H_{46}O_4$ for this product which are quite likely to be derived from the ketone (CCLXXXIX).

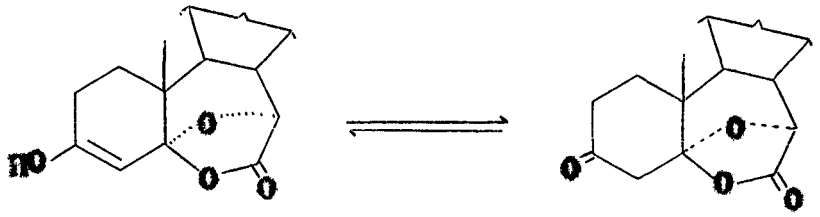
On the basis of spectral properties, most of the structures (CCXCVI-CCCI) can be discarded, since none of them possess an isolated methylene group adjacent to a carbonyl function as demanded by the n.m.r. spectrum (3.0d and 2.3d). Structures (CCXCVIII-CCC) show the presence of carbon-carbon double bond with one vinylic proton but the n.m.r. and i.r. spectra of the compound gave no indication of the presence of an α,β-unsaturated moiety. To mention further, a strong band at 1702 cm^{-1} can not be reconciled with the structures (CCXCVII-CCC). Strong bands at about 1800-1740 cm^{-1} were usually observed for cyclic anhydrides[107] such as in (CCCI), but this structure also lacks the presence of an isolated methylene group. With the elimination of the structures (CCXCVII-CCCI), the choice of the structures narrowed down to (CCXCIII) and (CCXCVI).

The n.m.r. signal at δ 5.5 may be confused with a vinylic proton. To make it clear, the Dreiding model of (CCXCIII) was examined which revealed that the dihedral angle between C_{7a}-$\underline{H}$ and C_{8}-$\beta\underline{H}$ is almost 90° and this led to the assignment of signal at δ 5.5 to C_{7a}-$\underline{H}$ in the compound (CCXCIII).

A possible mechanism for the formation of (CCXCIII) under the Baeyer-Villiger oxidation conditions can be proposed as in Scheme-1.

Scheme - 1





(CCXCIII)

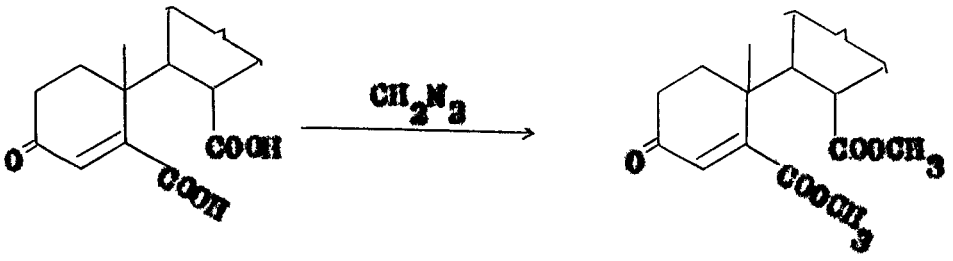
From the mechanistic as well as spectral considerations, the compound, m.p. 105° has been assigned the oxetolactone structure (CCXCIII). It is pertinent to suggest that the migration of a vinylic carbon (C_5) may occur in preference to C_7 to afford (CCXCIII). The strong bands in the i.r. spectrum of (CCXCIII) at 1793 and 920 cm^{-1} can be assigned to C=O and C-O-C linkage of the oxetolactone moiety.[108] The other strong band at 1720 cm^{-1} is attributed to C_3-keto function.

<u>Characterization of the compound m.p. 206° as 3-oxo-9,7-secostigmast-4-en-5,8-dicarboxylic acid (CCXCIV)</u>

The compound, m.p. 206° analysed for $C_{29}H_{46}O_5$ and thus showed an addition of three oxygen atoms to the starting ketone (CCLXXXIX) during the course of reaction. The i.r. spectrum of this compound showed bands at 3400-3200 br (C<u>O</u>O<u>H</u>), 1720 (<u>C</u>O<u>O</u>H) and 1680 cm^{-1} (C=C-C=O). The presence of dicarboxylic function in this compound was discernible from its n.m.r. spectrum. A broad multiplet ($W_{\frac{1}{2}}$ 14 Hz) at δ 11.03 was observed integrating

for two protons of the two carboxylic acid group and were found exchangeable with deuterium supporting the presence of acidic protons. The singlet at δ 6.7 integrating for one proton is ascribable to C_4-vinylic proton. This downfield shift of the vinylic proton is attributable to its being β - to the acid carbonyl function. The other signals at δ 3.5 and 2.20 as broad multiplet can be assigned[36] to a methine proton (C8-β H) and C2-H_2, respectively. Other signals were seen at δ 1.3 (C_{10}-CH_3), 0.76 (C_{13}-CH_3), 1.1 and 0.85 (other methyl groups).

To further substantiate the structure of the dicarboxylic acid (CCXCIV), the following chemical transformation was made which gave rise to the corresponding dimethyl ester (CCCII). This transformation obviously supports the presence of two carboxylic groups in the structure (CCXCIV), m.p. 206°.



(CCXCIV) (CCCII)

Dimethyl 3-oxo-6,7-secocholestan-4-en-5,8-dicarboxylate (CCCII)

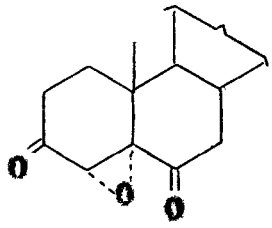
The compound (CCXCIV) on treatment with diazomethane afforded (CCCII), as an oil which was analysed for $C_{31}H_{50}O_5$. The i.r. spectrum of (CCCII) showed bands at 1725 ($\underline{COOCH_3}$), 1680 ($\underline{C=C-C=O}$), 1190 and 1170 cm^{-1} (methyl ester). The n.m.r. spectrum of this compound exhibited a singlet at δ 6.45 (1H) attributable to C4-vinylic proton. Two sharp singlets, integrating for three protons each, appeared at δ 3.81 and 3.63. The signals at δ 3.81 could be assigned to C_5-$COOC\underline{H}_3$ and other one at some higher field at δ 3.63 to C_8-$COOC\underline{H}_3$. A broad multiplet spread between δ 3.7-3.3 for three protons is ascribable to methine and methylene protons (C9-$\beta\underline{H}$ and C2-$\underline{H}_2$). Other signals were found at δ 1.2 (C_{10}-CH_3), 0.65 (C_{13}-CH_3), 0.87 and 0.78 (other methyls).

The notable feature of the n.m.r. spectrum of the compound (CCCII) is the downfield appearance of one of the two methoxy groups (C_5-$COOC\underline{H}_3$). This can be attributed to the presence of an α,β-unsaturated keto group of ring A in (CCCII). This further lends support to the structure (CCXCIV).

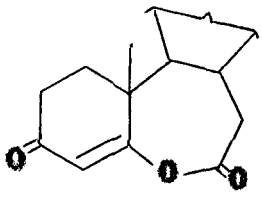
Characterization of the compound (CCXCV) as 4α,5α-oxidostigmastane-3,6-dione

The compound (CCXCV) obtained from the Baeyer-Villiger oxidation of the ketone (CCLXXXIX) as an oil, analysed for

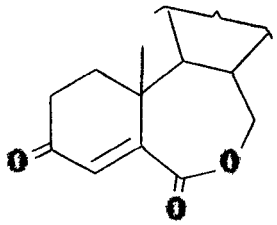
$C_{29}H_{46}O_3$. Addition of one oxygen to the substrate (CCLXXXIX) could lead to several possibilities such as (CCXCV - CCXCV-d).



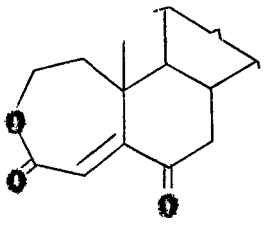
(CCXCV)



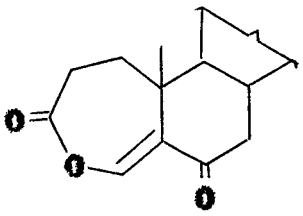
(CCXCV-a)



(CCXCV-b)



(CCXCV-c)



(CCXCV-d)

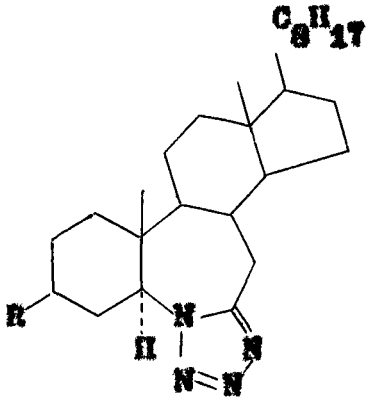
The i.r. spectrum of the compound gave significant bands at 1720, 1715 and 910 cm^{-1}. These values narrowed down the choice to only the epoxy[107] structure (CCXCV) as others would have shown different values having ϵ -lactone, ϵ -enol lactone and/or α,β -unsaturated carbonyl moieties. The n.m.r. spectrum of the compound was devoid of any vinylic proton which would have been discernible in case of others (CCXCV-a - d) except in the epoxy

structure (CCYCV). The n.m.r. spectrum of the compound exhibited signals at δ 3.7 (s, $W_{\frac{1}{2}}$ 2 Hz) which has been assigned[106] to $C_4\beta$-proton. Other signals were observed at δ 1.01 (C_{10}-CH_3), 0.7 (C_{13}-CH_3), 0.9 and 0.85 (other methyls). The formulation of the compound as α-epoxide has been suggested on the general understanding that the reaction occurs from the less sterically hindered α-side (back side) of the steroidal molecule. On the basis of the foregoing discussions and spectral values, this oily compound could be identified as 4α,5α-oxidostigmastane-3,6-dione (CCYCV).

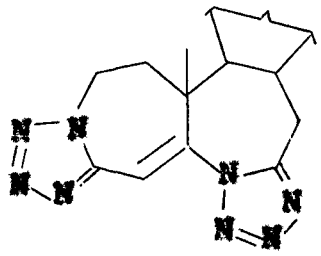
Steroidal Tetrazoles

The chemistry of steroidal tetrazoles in the preceding years has gained vital significance because of their biological activities. They also proved to be useful in many potential drugs. On the basis of this realization, a number of papers appeared in the recent past describing the preparation of tetrazoles from various steroidal ketones using an excess of hydrazoic acid and boron trifluoride-etherate as catalyst, a variant of Schmidt reaction.

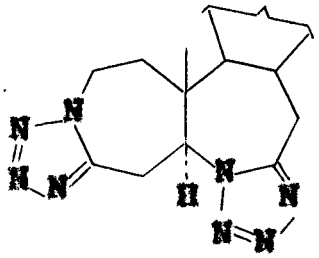
Several papers on the synthesis of steroidal tetrazoles, mainly in the cholestane series, have recently appeared from our laboratories. They include 6-aza-B-homo-5α-cholestano [6,7-d] tetrazole (CXLII), its 3β-acetoxy (CXLIII), 3β-chloro (CXLIV) and 3β-hydroxy (CXLVI) analogues,[63] 4,6-diaza-A,B-bishomo-5α-cholestano [3,4-d:6,7-d] bistetrazole (CCI), 3,6-diaza-A,B-bishomocholest-4a-eno [3,4-d:6,7-d] bistetrazole (CCVII), 3,6-diaza-A,B-bishomo-5α-cholestano [3,4-d:6,7-d] bistetrazole (CCI),[64] 6-aza-B-homocholesta-3,4-dieno [6,7-d] tetrazole (CCXI),[65] 6-aza-B-homo-5α-bromocholestano [6,7-d] tetrazole (CCXVII), its 3β-acetoxy analogue (CCXIX), 6-aza-B-homocholest-4-eno [6,7-d] tetrazole (CCXVIII) and its 3β-acetoxy analogue[67] (CCXX) reported from our laboratories in the recent past.



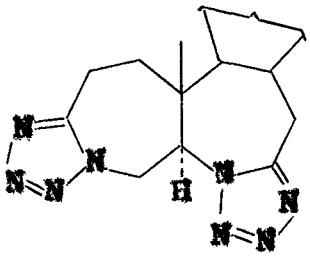
(CXLII) R, H
(CXLIII) R, OAc
(CXLIV) R, Cl
(CXLVI) R, OH



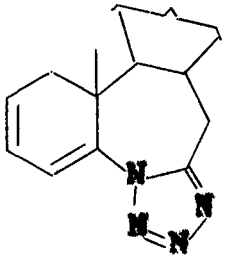
(CCVII)



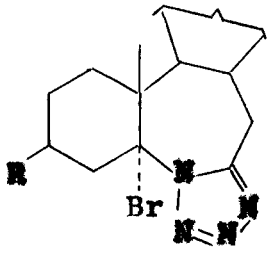
(CC)



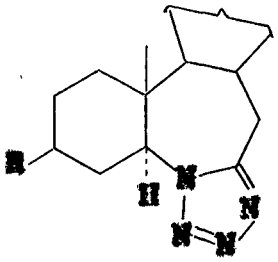
(CCI)



(CCXI)

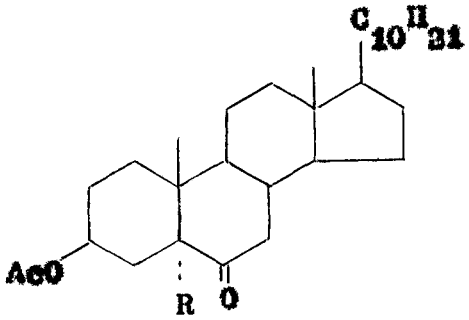


(CCXVII) R, H
(CCXIV) R, OAc

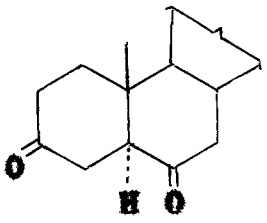


(CCXVIII) R, H
(CCXX) R, OAc

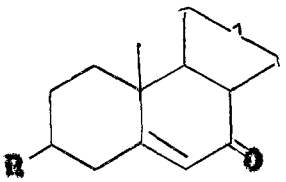
In this chapter, an attempt has been made to synthesise some hitherto unreported tetrazoles from the saturated and α,β -unsaturated steroidal ketones of the stigmastane series. The substrates treated with an excess of hydrazoic acid and boron trifluoride-etherate for this reaction were 3β-acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII), 3β-acetoxy-5α-stigmastan-6-one (XLII), 5α-stigmastane-3,6-dione (CCCIII), stigmast-5-en-7-one (CCCIV), its 3β-acetoxy (CCCV), 3β-chloro (CCCVI) and 3β-hydroxy (CCCVII) analogues, respectively.



(CCLXXXVIII) R, Br
(XLII) R, H

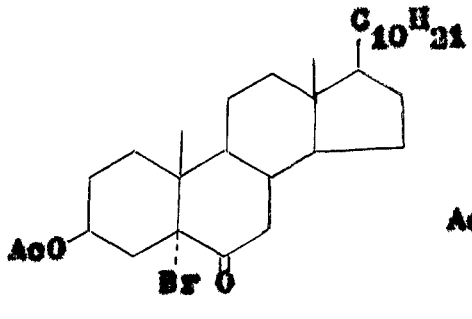


(CCCIII)

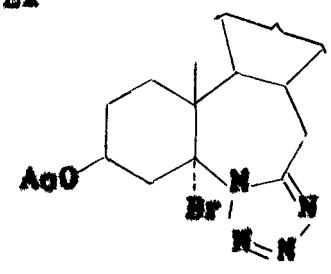


(CCCIV) R, H
(CCCV) R, OAc
(CCCVI) R, Cl
(CCCVII) R, OH

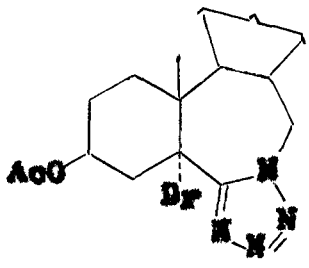
Reaction of 3β-acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII) with an excess of hydrazoic acid



(CCLXXXVIII)



(CCCVIII)



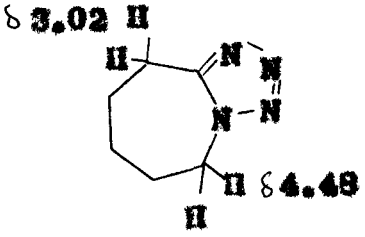
(CCCIX)

3β-Acetoxy-5α-bromostigmastan-6-one (CCLXXXVIII) was treated with an excess of hydrazoic acid solution, prepared by the method described by Moural and Sykora[53] in the presence of boron trifluoride-etherate as catalyst. The reaction mixture was worked up in the usual manner after a period of two weeks and was chromatographed over silica gel. The column chromatography of the reaction mixture provided a compound, m.p. 146°.

Characterization of the compound, m.p. 146° as 3β-acetoxy-5α-bromo-6-aza-5-homostigmastano [6,7-d] tetrazole (CCCVIII)

The compound, m.p. 146°, analysed for $C_{31}H_{51}N_4Br$ (positive Beilstein test). Its elemental analysis showed the addition of four nitrogen atoms to the substrate (CCLXXXVIII). The i.r. spectrum of the compound, m.p. 146°, gave bands at 1720, 1525, 1450, 1370, 1235, 1030 and 740 cm^{-1}. The band at 1720 cm^{-1} may be due to acetate carbonyl and those at 1235 and 1030 cm^{-1} can be assigned to acetate and C-O stretchings. In the light of the earlier report,[54] the band at 1525 cm^{-1} is due to C=N stretching and those at 1450 and 1370 cm^{-1} are attributed to N=N stretching. The sharp band at 740 cm^{-1} is ascribable to C-Br stretching. On the basis of its elemental composition and i.r. values, two isomeric structures (CCCVIII) and (CCCIX) may be formulated for the compound, m.p. 146°. The clear differentiation between the two possible isomers can be made by its n.m.r. spectrum.

Dilaio and Permutti[100] has reported that the n.m.r. spectrum of the tetrazole (CXLIII) showed a two-proton multiplet at δ 4.48 which is assigned to the methylene group directly attached to the ring nitrogen atom and another two-proton multiplet at δ 3.02 due to the methylene group adjacent to C=N fragment of the tetrazole system.



(CXLIII)

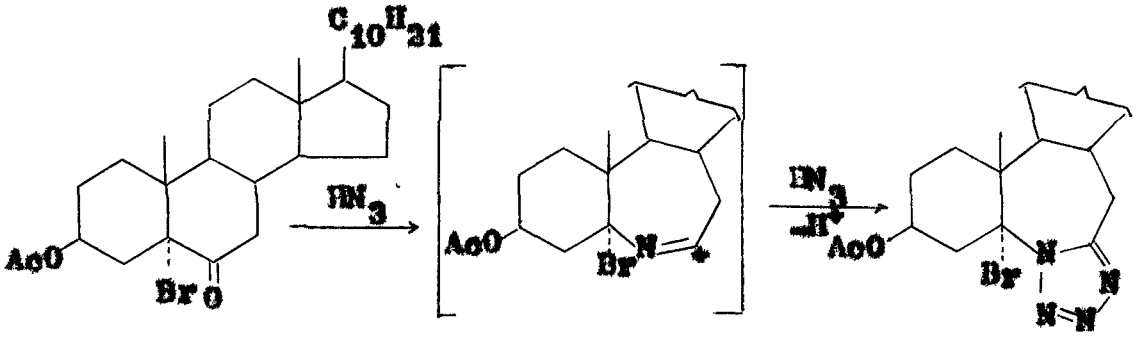
The n.m.r. spectrum of the compound, m.p. 146° exhibited a broad peak integrating for one proton with $W_{\frac{1}{2}}$ 10 Hz at δ 5.25. This signal is assigned to its C3-α-proton (axial). The appearance of a broad signal for C3-α proton (axial) reveals that A/B ring junction is trans (C3α-Br). Another significant signal, throwing light on the structure of the compound, appeared at δ 3.5 as a multiplet integrating for two protons and has been assigned to C7a-protons (C7a-H_2). This value shows that the grouping $-N=C(-N)-CH_2$ is present which is compatible with the structure (CCCVIII) only. The isomeric structure (CCCXIX) would have exhibited signal for C7a-protons (C7a-H_2)

at about δ 4.5.[109] The acetate methyl signal was observed as a singlet at δ 2.03. Other methyl signals were observed at δ 0.9, 0.86 and 0.66.

There seems to be some points of contrast between this tetrazole (CCCVIII) and the many other analogous obtained in the cholestane series as far as n.m.r. spectral behaviour is concerned. In the cholestane series[63,64] only one of the CH_2-protons was discernible at about δ 3.2 and the other merged with the methylene envelope. Further C_{13}-Me signal appeared at a much higher field (δ 0.4 - 0.5) in most of the cases.[56,63,64,67] An explanation for these observations was advanced by the earlier workers. In the present case, the tetrazole (CCCVIII) showed both the CH_2-protons in the discernible area (δ 3.5) and that C_{13}-Me signal appeared at δ 0.63 which is rather normal for this methyl group as in other steroid derivatives. There was no appreciable diamagnetic shift associated with this signal as has been observed for analogous cholestane tetrazoles. There seems to be no easy explanations for this discrepancy between the analogous cholestane and stigmastane tetrazole except that the side chain in the two has different "long range effect."

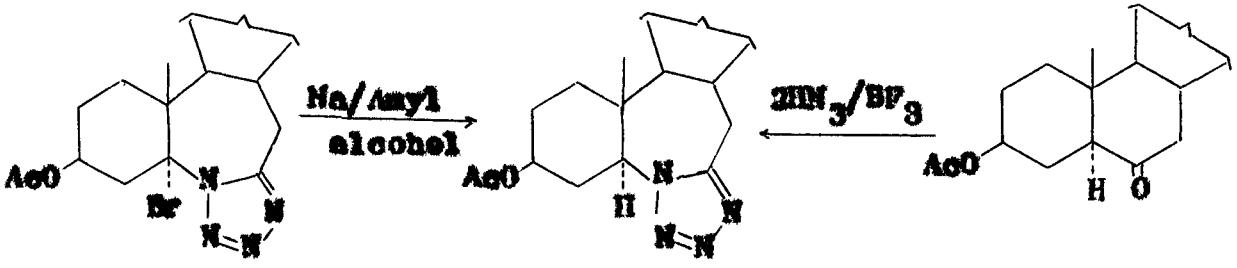
On the basis of the above discussions and spectral behaviour, the compound, m.p. 146° may be characterised as 3β-acetoxy-5α-bromo-6-aza-B-homostigmastano [6,7-d] tetrazole (CCCVIII).

The formation of 6:7 fused tetrazole is expected to involve the intermediacy of imidocarbonium ion (A) as shown below.



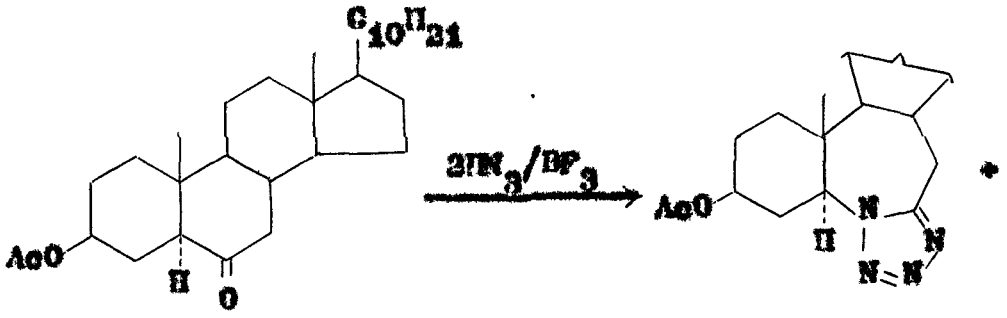
(CCLXXXVIII) (A) (CCCVIII)

The compound (CCCVIII) on sodium-pentyl alcohol reduction afforded (CCCX). It was found to be identical in all respects (t.l.c., m.p., m.m.p. and spectral data) with an authentic sample of (CCCX) obtained from the reaction of (XLII) with an excess of hydrazoic acid.



(CCCVIII) (CCCX) (XLII)

Reaction of 3β-acetoxy-5α-stigmastan-6-one (XLII) with an excess of hydrazoic acid: 3β-Acetoxy-6-aza-B-homo-5α-stigmastano [6,7-d] tetrazole (CCCX) and 3β-acetoxy-6-aza-B-homo-5α-stigmastan-7-one (CCCXI)



(XLII) (CCCX)

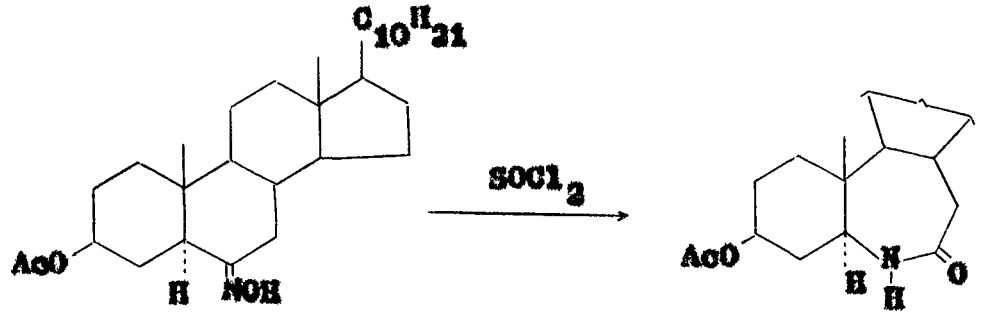
(CCCXI) (CCCXII)

Treatment of 3β-acetoxy-5α-stigmastan-6-one (XLII) with an excess of hydrazoic acid provided after usual work up and column chromatography two compounds, m.ps. 170° and 253°.

Characterisation of the compound, m.p. 170° as 3β-acetoxy-6-aza-B-homo-5α-stigmastano [6,7-d] tetrazole (CCCX)

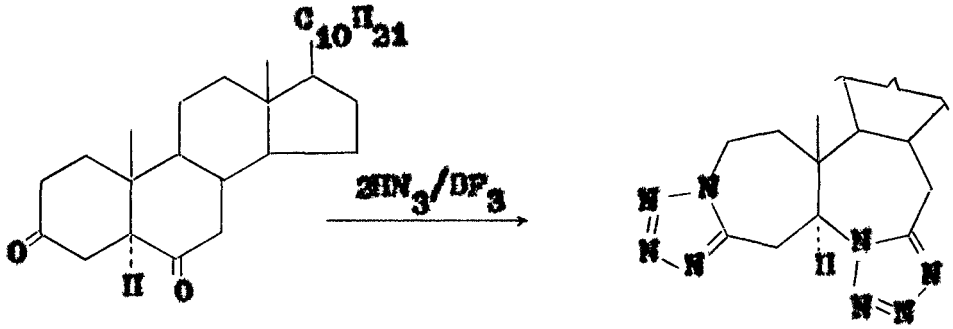
The compound, m.p. 170° analysed for $C_{31}H_{53}N_4O_2$ and showed bands in its i.r. spectrum at 1730 (CH_3-CO-O), 1360 and 1240 cm^{-1} (acetate). The tetrazole bands were observed at 1530, 1450 and 1370 cm^{-1}. The n.m.r. spectrum of the compound (CCCX) gave signals at δ 4.81 br (1H, C_3-α-H axial, $W_{\frac{1}{2}}$ 14 Hz), 4.29dd (1H, C_5-αH; JC_5-αH; C_4-βH 8 Hz; C_5-αH; C_4-αH 2Hz), 3.43 dd (J 15 Hz, C_{7a}-H$_2$) and 2.01s (acetate methyl). The broad signal of C_3-α axial proton indicates that the A/B ring junction is trans. Other signals were observed at δ 0.55s (C_{13}-Me), 0.91, 0.83 and 0.65 (methyl protons). The isomeric structure (CCCXII) is disfavoured as n.m.r. pattern of this compound is not agreeable with this structure.

The compound (CCCXI), m.p. 253° analysed for $C_{31}H_{53}NO_3$ showed bands in its i.r. spectrum at 3350 (NH), 1730 (CH_3-CO-O), 1660 (-CONH) and 1240 cm^{-1} (acetate). The elemental analysis and i.r. data of this compound indicates the presence of a lactam moiety in it. The same compound, m.p. 253° was also obtained by the Beckmann rearrangement of (CCCXIII)[41]. The two samples of (CCCXI) obtained from the two sources were found to be identical (m.p., m.m.p., t.l.c. and spectral data).

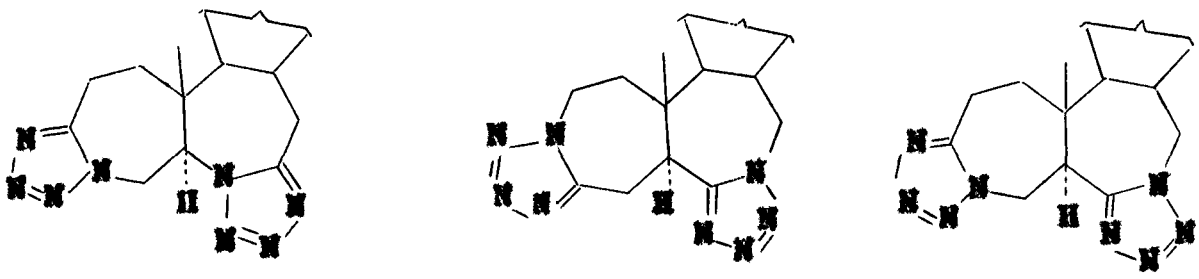


(CCCXIII) (CCCXI)

Reaction of 5α-etiallocholane-3,6-dione (CCCIII) with an excess of hydrazoic acid: 3,6-Diaza-A,B-bishomo-5α-etiallocholano [3,4-d:6,7-d] bistetrazole (CCCXIV)



(CCCIII) (CCCXIV)

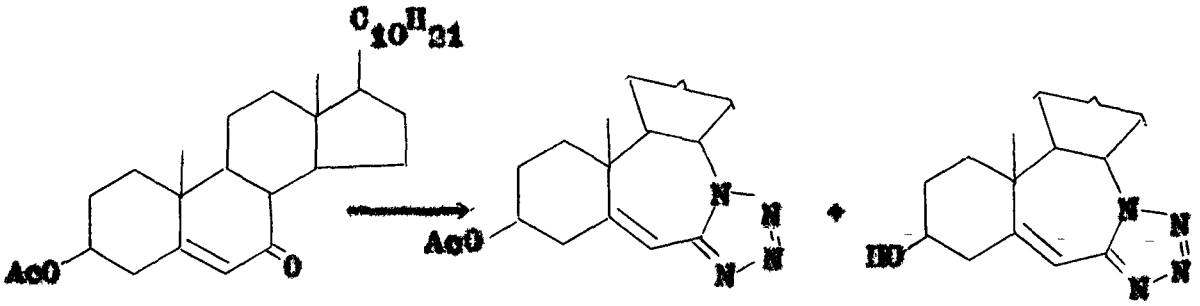


(CCCXV) (CCCXVI) (CCCXVII)

The ketone (CCCIII) was treated with an excess of hydrazoic acid in the presence of boron trifluoride-etherate as catalyst, which after usual work up and column chromatography over silica gel provided a single compound, m.p. 305°. The compound, m.p. 305° analysed for $C_{29}H_{48}N_8$ which showed the addition of eight nitrogen atoms to the substrate (CCCIII). Its i.r. spectrum exhibited the characteristic bands for tetrazole moiety at 1530, 1470 and 1380 cm^{-1} (C=N, N=N). By virtue of two ketonic functions in the substrate (CCCIII), four combinations for bistetrazole are conceivable (CCCXIV-CCCVII). Of them, the one considerable here is 3,6-diaza-A,B-bishomo-5α-stigmastano [3,4-d:6,7-d] bistetrazole (CCCXIV). The bistetrazole (CCCXIV), having 6-azatetrazole moiety was supported by its n.m.r. spectrum in preference to its 7-aza-structures (CCCXVI) and (CCCXVII). This consideration rests partly on the observation[63] of the formation of 6-azatetrazoles from 6-oxosteroids by preferential migration of a tertiary C-5 relative to secondary C-7. The n.m.r. spectrum of the compound, m.p. 305° gave a doublet centred at δ 3.25 (J 15 Hz) integrating for one proton which, in the light of earlier assignments,[62,63] could be ascribed to one of the C_{7a}-protons. It was further supported by the diamagnetic shift of C_{13}-methyl protons at δ0.45 which is characteristic of the 6-azatetrazole system.[62] Thus 6-aza-B-homo [6,7-d] tetrazole moiety may be a unit of

the other alternative structures (CCCXIV) and (CCCXV). The difference might exist in ring A where C_3-keto group is flanked on either side by two methylenes of equal migratory aptitude. Thus the possibility of 7-aza isomer (CCCXVI) and (CCCXVII) can be excluded on the basis of earlier findings.[63,63] The structure of bistetrazole having 3-azatetrazole moiety as in (CCCXIV) could be prefered over its 4-aza isomer (CCCXV) on the basis of its n.m.r. spectrum. A doublet was observed at δ4.83 which may be assigned to C_5-$\alpha\frac{1}{3}$ H (J 7 Hz). A multiplet centred at δ 4.6 was assigned to C_5-$\alpha\frac{1}{2}$ H, C_3-H_3 and C_{4a}-H (equatorial). Another doublet at δ 4.1 (J 10 Hz) which on the basis of the work of Dillaio[109] and Ahmad et al.,[63,64] could be attributed to C_{4a}-H (axial) of the tetrazole bearing 6-aza structure (CCCXIV). Other methyl signals were observed at δ1.2 (C_{10}-CH_3), 0.45 (C_{13}-CH_3), 0.86 and 0.78. On the basis of foregoing discussions and spectral evidences, the compound, m.p. 305° may be identified as 3,6-diaza-A,B-bishomo-5α-stigmastano [3,4-d:6,7-d] bistetrazole (CCCXIV).

Reaction of 3β-acetoxystigmast-5-en-7-one (CCCV) with hydrazoic acid



(CCCV) (CCCXIX) (CCCXXI)

The ketone (CCCV) on treatment with an excess of hydrazoic acid following the usual method provided two compounds, m.ps. 156° and 186°.

Characterisation of the compound, m.p. 156° as 3β-acetoxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXIX)

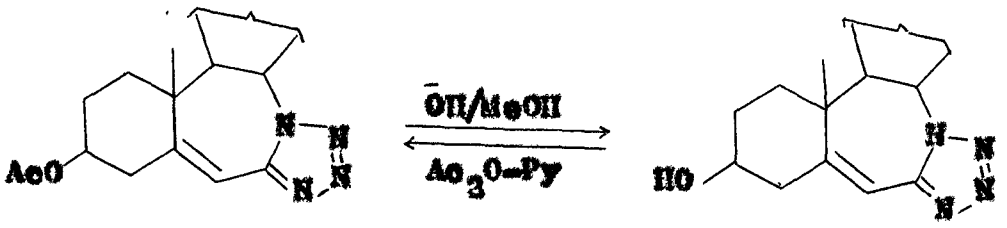
The compound, m.p. 156° was found, by its elemental analysis, compatible with molecular composition as $C_{31}H_{50}N_4O_3$ which confirms the presence of four nitrogen atoms in it. Its u.v. spectrum gave absorption maxima at 240 nm ($\log \epsilon$ 4.02). The i.r. spectrum of this compound showed bands at 1735 (CH_3-CO-O), 1660 (C=C) and 1250 cm^{-1} (acetate). The tetrazole peaks were obtained at 1510, 1460 and 1370 cm^{-1}. The n.m.r.

spectrum of this compound gave signals at δ 6.53s (1H, C_6-vinylic proton), 4.75 br (1H, $W_{\frac{1}{2}}$ 20 Hz, C_3-αH, axial), 4.2br (1H, N-C_8-βH), 3.03s (3H, CH_3COO), 1.2s (C_{10}-CH_3), 0.78s (C_{13}-CH_3), 0.87 and 0.78 (other methyl protons). The spectral behaviour of this compound, m.p. 156° was found to be in good agreement with the corresponding tetrazole (CLXXX) in the cholestane series.[59] Thus on the basis of spectral evaluation, the compound, m.p. 156° can be identified as 3β-acetoxy-7a-aza-B-homoetiocast-5-eno [7a,7-d] tetrazole (CCCXIX).

Characterisation of the compound, m.p. 186° as 3β-hydroxy-7a-aza-B-homoetiocast-5-eno [7a,7-d] tetrazole (CCCXXI)

The compound m.p. 186° analysed for $C_{20}H_{48}N_4O$. Its u.v. spectrum showed absorption maxima at 245 mm ($\log \epsilon$ 4.05) and its i.r. peaks were observed at 3300 br (OH), 1665 (C=O), 1505, 1470 and 1380 cm^{-1} (C=N, N=N). Its n.m.r. spectrum gave signals at δ 6.51s (1H, C_6-vinylic proton), 4.23 br (1H, N-C_8-βH), 3.75 br (1H, $W_{\frac{1}{2}}$ 24 Hz, C_3-αH, axial), 1.33s (C_{10}-CH_3), 0.83s (C_{13}-CH_3), 1.0 and 0.93 (other methyl groups). The hydroxy proton resonance was not clearly discernible. On spectral evidence, the compound, m.p. 186° was characterized as 3β-hydroxy-7a-aza-B-homoetiocast-5-eno [7a,7-d] tetrazole (CCCXXI). The hydroxy tetrazole (CCCXXI) was conveniently converted into its 3β-acetate analogue (CCCXIX) by Ac_2O-pyridine.

Base hydrolysis of 3β-acetoxy-7a-aza-B-homostigmast-5-ene [7a,7-d] tetrazole (CCCXIX)

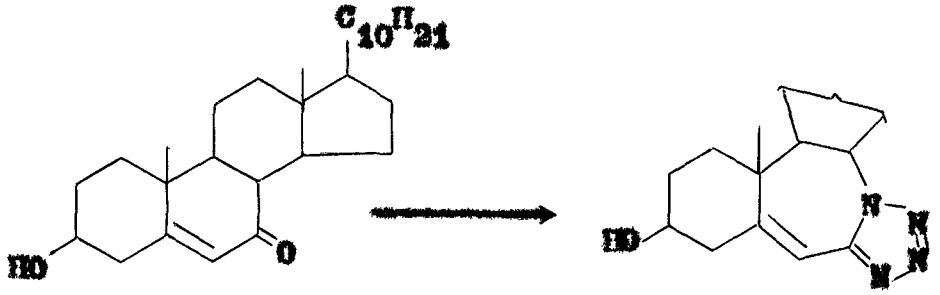


(CCCXIX) (CCCXXI)

In anticipation of obtaining the compound (CCCXXI), the tetrazole (CCCXIX) was subjected to hydrolysis under basic conditions which eventually afforded a compound, m.p. 166°. The spectral pattern, t.l.c. and m.p. corresponded to one of the compounds obtained from the reaction of ketone (CCCV) with an excess of hydrazoic acid. It is then believed that the acetate function in (CCCXIX) was hydrolysed during the course of the reaction. This chemical transformation further supported the compound, m.p. 186° as 3β-hydroxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXXI).

A sample of the hydroxy tetrazole (CCCXXI) was also obtained by subjecting 3β-hydroxystigmast-5-en-7-one (CCCVII) to the reaction with an excess of hydrazoic acid.

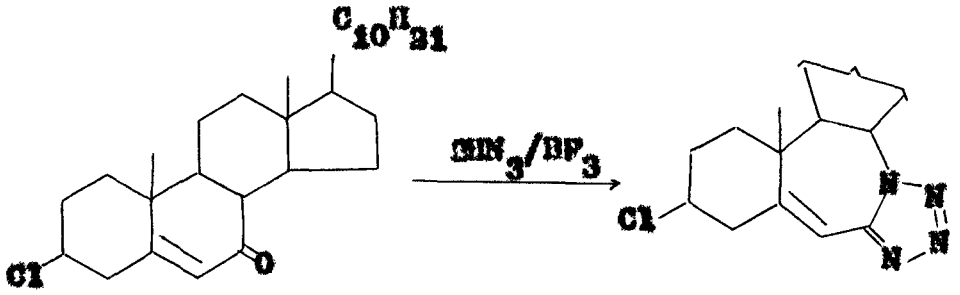
Reaction of 3β-hydroxystigmast-5-en-7-one (CCCVII) with hydrazoic acid



(CCCVII) (CCCXXI)

The ketone (CCCVII) on treatment with an excess of hydrazoic acid afforded, after work up and column chromatography, a compound, m.p. 180°. This compound was compared with that obtained from the reaction of the ketone (CCCV), as one of its reaction products and found identical in all respects (t.l.c., m.p., m.m.p. and spectral data) which was identified as 3β-hydroxystigmast-5-eno [7a,7-d] tetrazole (CCCXXI).

Reaction of 3β-chlorostigmast-5-en-7-one (CCCVI) with an excess of hydrazoic acid



(CCCVI) (CCCXX)

The ketone (CCCVI) was allowed to react with hydrazoic acid which after usual work up and column chromatography afforded a single compound, m.p. 180°.

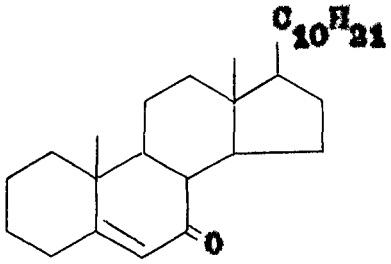
Identification of the compound, m.p. 180° as 3β-chloro-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXX)

The compound, m.p. 180 analysed correctly for $C_{29}H_{47}N_4Cl$ (positive Beilstein test). Its i.r. spectrum exhibited bands at 1670 (C=C), 1515, 1465 and 1380 cm^{-1} (C=N, N=N). A sharp band at 770 cm^{-1} was seen which is assigned to C-Cl stretching. The n.m.r. spectrum of this compound gave signals at δ 6.3s (1H, C_6-vinylic proton), 4.1br ($W_{\frac{1}{2}}$ 20 Hz, C_3-αH, and C_8-βH),

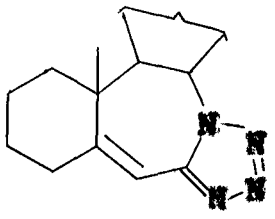
2.7d (C_4-H_2), 1.3s (C_{10}-CH_3), 0.8s (C_{13}-CH_3), 0.85 and 0.9 (other methyl groups). On the basis of the spectral evidence, the compound m.p. 180° can be characterized as 3β-chloro-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXX).

Reaction of stigmast-5-en-7-one (CCCIV)

The ketone (CCCIV) when treated with an excess of hydrazoic acid furnished a compound, m.p. 140°.



(CCCIV)



(CCCXVIII)

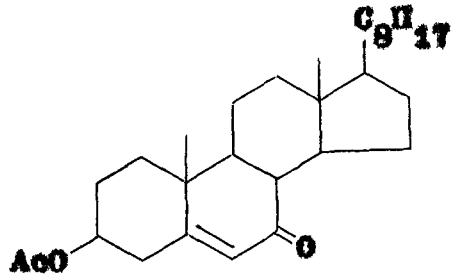
Characterization of the compound, m.p. 140° as 7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXVIII)

The compound, m.p. 140° analysed for $C_{29}H_{48}N_4$ gave peaks in its i.r. spectrum at 1665 (C=C), 1510, 1450 and 1380 cm^{-1} (C=N, N=N). The n.m.r. spectrum of this compound exhibited signals at δ 6.4s (C_6-vinylic proton) and a broad signal at

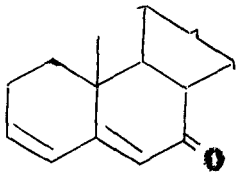
δ 4.2 ($W\frac{1}{2}$ 10 Hz) ascribable to C_3-βH. The methylene envelope was present in the region of δ 2.2-2.4. Other methyl protons gave signals at δ 1.2, 0.9 and 0.8. The foregoing discussion supported the structure of the compound, m.p. 140° as 7a-aza-B-homoestigmast-5-eno [7a,7-d] tetrazole (CCCXVIII).

Azasteroids

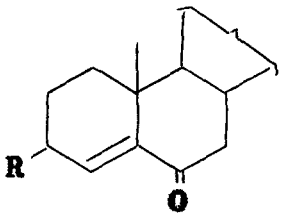
Several papers dealing with the preparation of azasteroids from various steroidal ketoximes belonging mainly to the cholestane series have appeared from our laboratories. The most common and facile method for the synthesis of steroidal lactams are the Beckmann rearrangement and Schmidt reaction. The azasteroids were synthesised from 3β-acetoxycholest-5-en-7-one (XCVIII),[110] and cholesta-3,5-dien-7-one[111](CV), 3β-acetoxycholest-4-en-6-one[112] (LXXXVI), cholest-4-en-6-one[113] (LXXX) and 3α,5-cyclo-5α-cholestan-6-one[114] (XVII).



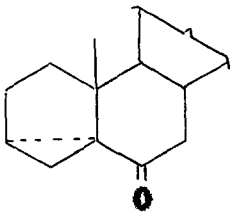
(XCVIII)



(CV)



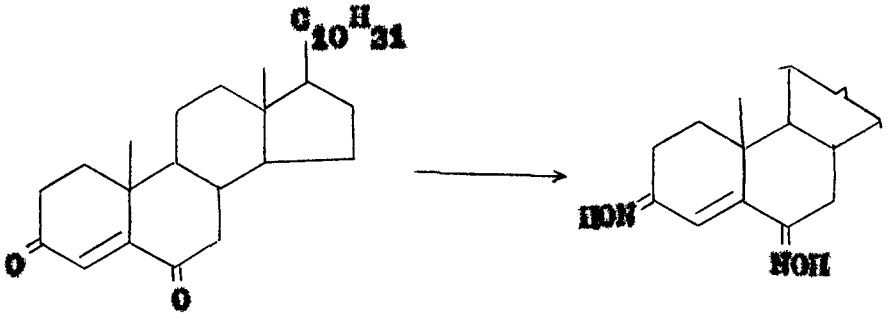
(LXXXV) R, OAc
(LXXX) R, H



(XVII)

In the light of the above work,[110-114] attempts were made to prepare lactams from easily accessible steroidal ketoximes from the stigmastane series. For this, stigmast-4-ene-3,6-dione oxime (CCCXXII) was subjected to the conditions of Beckmann rearrangement.

Oximation of stigmast-4-ene-3,6-dione (CCLXXXIX)



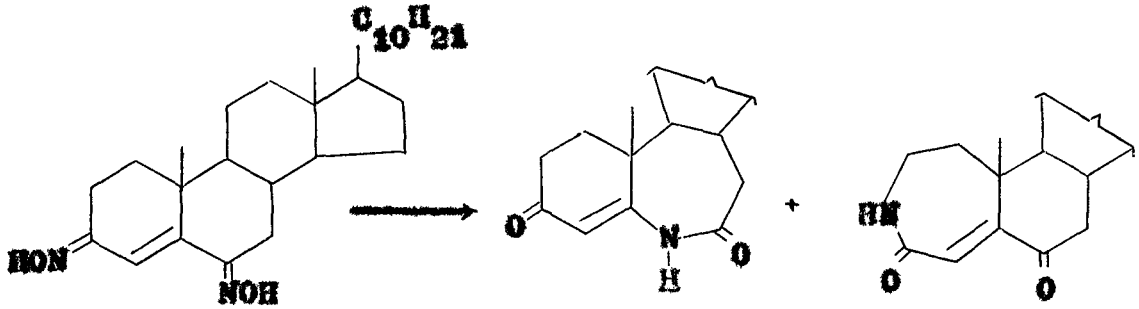
(CCLXXXIX) (CCCXXII)

The diketone (CCLXXXIX) was subjected to oximation following usual procedure[115] which gave a compound, m.p. 195°. The compound, m.p. 195° was analysed for $C_{29}H_{48}N_2O_2$. Its i.r. spectrum gave bands at 3310-3300 br (N-OH), 1660 cm^{-1} (C=N). The spectrum was devoid of any absorption in the region of 1600-1800 cm^{-1} indicating that the two keto groups of the substrate (CCLXXXIX) have been changed into its corresponding dioxime. The n.m.r. spectrum of the compound, m.p. 195°

exhibited signals at δ 6.9s (C_6-vinylic proton), 6.5br (2H, N-OH), 3.3m (C_2-H_2 and C_7-H_2). The methyl protons were observed at δ 1.3, 0.98, 0.87 and 0.75. On the basis of these spectral values and molecular composition, the compound, m.p. 195° can safely be identified as stigmast-4-ene-3,6-dione oxime (CCCXXII).

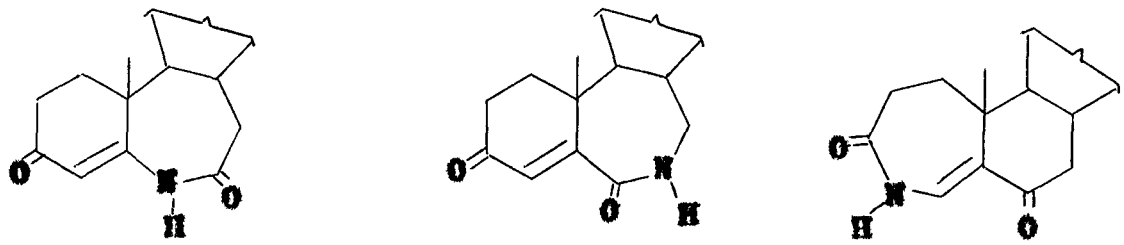
Beckmann rearrangement of stigmast-4-ene-3,6-dionoxime (CCCXXII)

The Beckmann rearrangement of the dioxime (CCCXXII) with thionyl chloride followed by column chromatography over silica gel,[116] afforded two compounds, m.ps. 152° and 210°.

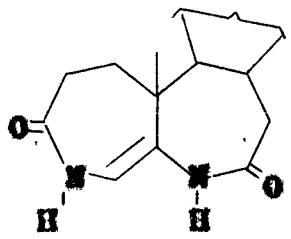


(CCCXXII) (CCCXXIII) (CCCXXIV)

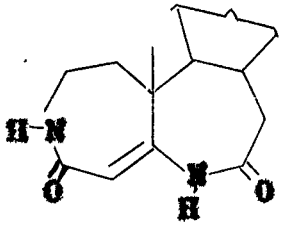
Characterisation of the compound, m.p. 152° as 6-aza-B-homostigmast-4-ene-3,7-dione (CCCXXIII)



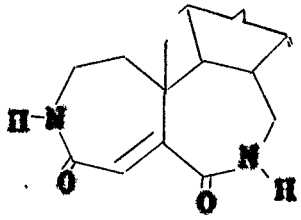
(CCCXXIII) (CCCXXV) (CCCXXVI)



(CCCXXVII)



(CCCXXVIII)



(CCCXXIX)

The compound, m.p. 152° analysed for $C_{29}H_{47}NO_2$. The molecular composition showed that a monolactam was formed. The i.r. spectrum of the compound, m.p. 152° gave bands at 3260 br (CO-NH), 1665 and 1620 cm^{-1} ascribable[117,118] to O=C-NH-C=C-C=O moiety. The i.r. values are compatible with the possible monolactam structures (CCCXXIII-CCCXXVI) formulated for this compound. The n.m.r. spectrum was found helpful in distinguishing them. Its n.m.r. spectrum displayed a broad signal at δ 6.9 integrating for one proton which, in the light of earlier observations,[110-114] can be assigned to NH proton of the lactam moiety in the proposed structure (CCCXXIII). A singlet for C_4-vinylic proton was observed at δ 5.9. A broad multiplet was seen at δ 2.2-2.4 ascribable to C_3-H_2 and C_7-H_2 protons.[117] The methyl signals were found at δ 1.2, 1.1, 0.9 and 0.8. The alternate 7-aza-structure (CCCXXV) is disfavoured because in that case C7a-methylene protons would have been observed[106,117] at δ 3.8-3.3 as multiplet. Further, the

possibility of 4-aza structure (CCCXXVI) is also ruled out because N-H and C_{4a}-vinylic protons would have appeared as doublet. The formation of dilactams (CCCXXVII-CCCXXIX) are also discarded on the basis of molecular composition and spectral properties. Thus on the basis of foregoing discussion, the compound, m.p. 152° can be characterised as 6-aza-D-homo-stigmast-4-ene-3,7-dione (CCCXXIII).

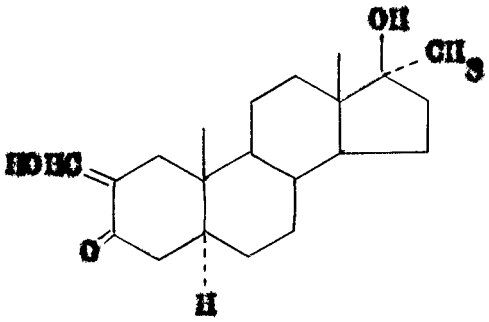
Characterization of the compound, m.p. 210° as 3-aza-A-homostigmast-4a-ene-4,6-dione (CCCXXIV)

The compound, m.p. 210° analysed for $C_{29}H_{47}NO_2$. The i.r. spectrum of this compound gave bands at 3250 (CO-NH), 1660 and 1585 cm^{-1} and these could be assigned to lactam moiety. The 3-aza-structure (CCCXXIV) formulated for this compound, finds support from its n.m.r. spectrum. The n.m.r. spectrum of this compound exhibited a broad singlet at δ 6.4 ascribable to C_{4a}-vinylic proton. A broad multiplet at δ 6.9 was assigned to N-H proton and the C_2-methylene protons were observed as multiplet at δ 2.88. A distorted doublet was observed at δ 2.25 which can be assigned to C_7-H_2 as in the structure (CCCXXIV). Its alternate 4-aza structure (CCCXXVI) can be discarded on the basis of its n.m.r. spectrum where a doublet would have been found for C_{4a}-H as observed for its

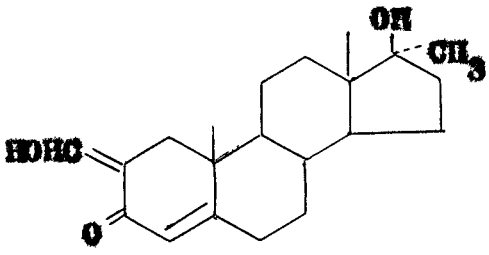
analogous lactam in the cholestane series.[117,119] Furthermore, in structure (CCCXXVI), the C_3-$\underline{H}_2$ and C_7-$\underline{H}_2$ protons would have been merged at δ 2.3-2.5. But the presence of multiplet at δ 2.83 could be accounted for by N-C_3-methylene protons supporting the structure (CCCXXIV) while discarding (CCCXXVI). Thus on the basis of the i.r. and n.m.r. spectra, the compound, m.p. 210° may be characterized as 3-aza-A-homostigmast-4a-ene-4,6-dione (CCCXXIV).

Steroidal Pyrazoles

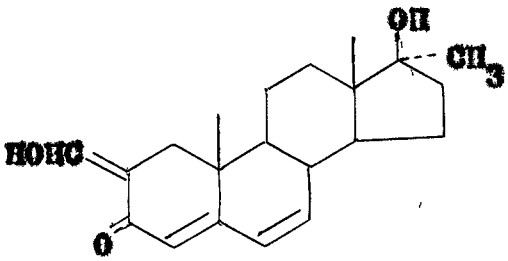
In recent years, the synthesis of steroidal pyrazole derivatives has attracted the attention of organic chemists because of the remarkable and unusual physiological activity and profound endocrinological interests associated with them. Since many drugs and dyes contain the pyrazole nucleus, the fusion of a pyrazole ring to steroidal nucleus may hold promise for many potential drugs. The unusual anabolic activity observed in humans,[91] attached vital significance with such compounds in steroids. As a result of this realization, synthesis of steroidal pyrazoles became a matter of much interests and consequently some papers appeared[90-104] in the recent past dealing with their preparation from various steroidal ketones. The different group of workers employed hydrazine and phenyl hydrazine as the reagent and the substrates included 2-hydroxymethylene-17α-methyl-5α-androstan-17β-ol-3-one (CCXXXII), 3-hydroxymethylene-17α-methylandrost-4-en-17β-ol-3-one (CCXXXIII), 2-hydroxymethylene-17α-methylandrost-4,6-diene-17β-ol-3-one (CCXXXIV),[90] 16$_\alpha$,17-epoxypregnenolone (CCXLIV),[93] 20-ethoxy-21-formyl-17β-pregna-14,20-diene (CCXLIV),[99] 3β-acetoxypregna-5,16-diene-20-one (CCLXVIII) and pregna-4,16-diene-3,20-dione (CCLXIX),[100,101] and 17-substituted-16,17-androstene (CCLXXVI).[103]



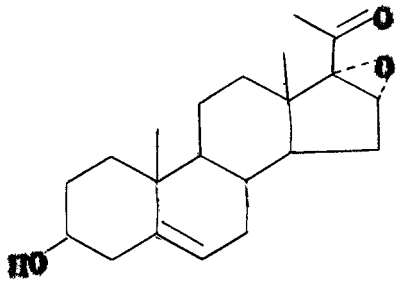
(CCXXXII)



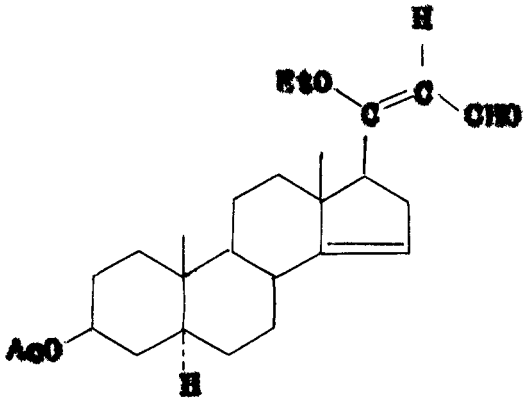
(CCXXXIII)



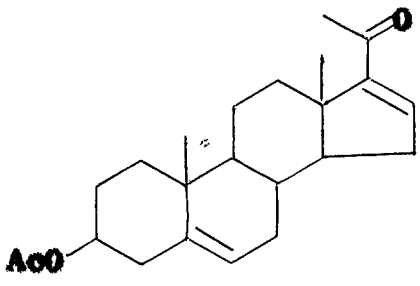
(CCXXXIV)



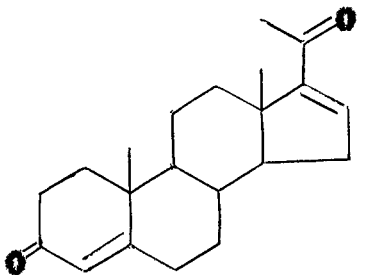
(CCXLIV)



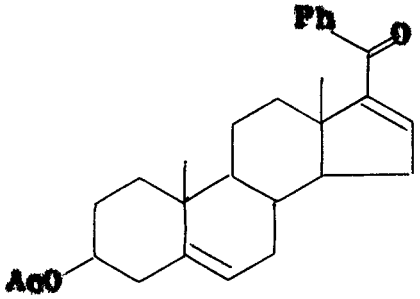
(CCLXIV)



(CCLXVIII)

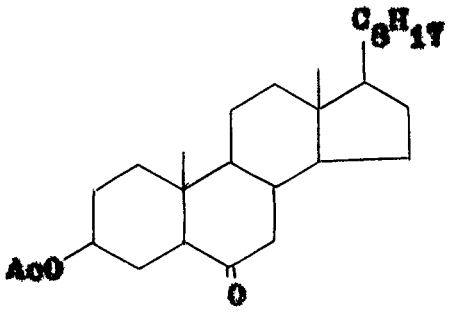


(CCLXIX)

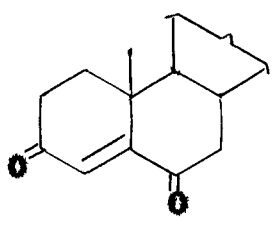


(CCLXXVI)

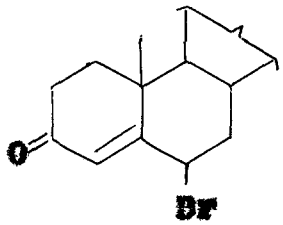
It is worth mentioning here that little attention has been paid towards the synthesis of such compounds in the cholestane series. Inspired by the results obtained by earlier workers,[91-102,119] we made attempts to synthesize steroidal pyrazoles from α,β-unsaturated ketones belonging to the cholestane series. In the light of earlier observations,[91-102,119] we subjected the easily accessible ketones such as 3β-acetoxy-cholest-4-en-6-one (LXXXVI), cholest-4-ene-3,6-dione (XCII), 6β-bromocholest-4-en-3-one (LXXVI) and cholest-4-en-3-one (LI) to the reaction of phenylhydrazine in the presence of acetic acid. At this stage the present work is primarily of exploratory nature.



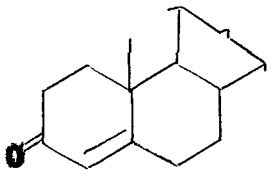
(LXXXVI)



(XCII)

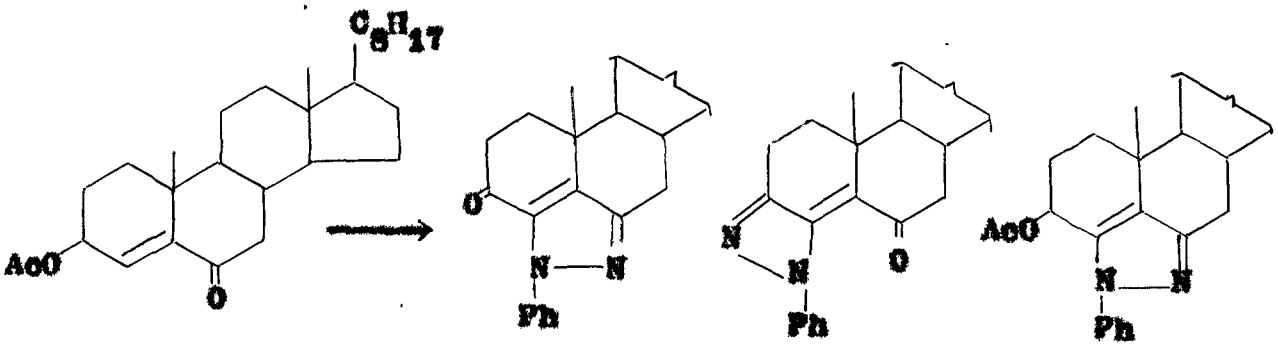


(LXXVI)



(LI)

Reaction of 3β-acetoxycholest-4-en-6-one (LXXXVI) with phenylhydrazine



(LXXXVI) (CCCXXX) (CCCXXXI) (CCCXXXII)

The ketone (LXXXVI) on treatment with phenylhydrazine in the presence of glacial acetic acid afforded after usual work up and column chromatography over silica gel a single compound, m.p. 226°.

Characterization of the compound, m.p. 226° as cholest-3-oxo-4-ene [4,6-d]-3'-phenylpyrazole (CCCXXX)

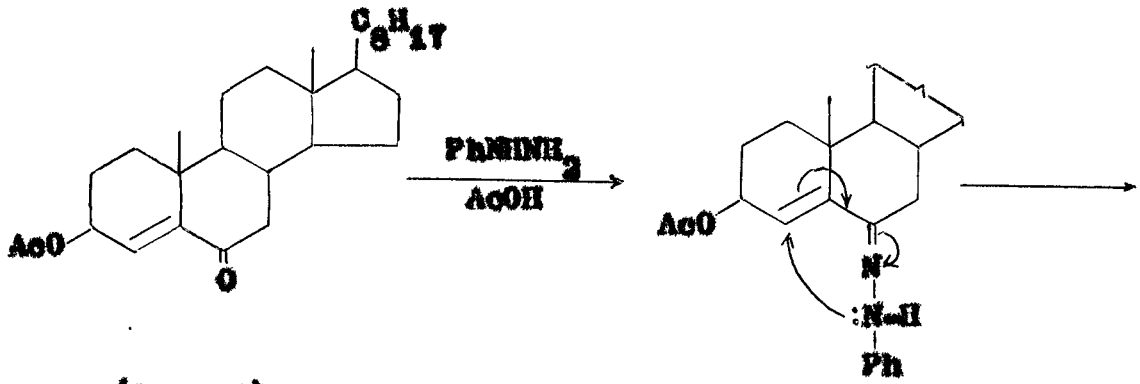
The compound, m.p. 226° was analysed for $C_{33}H_{46}N_2O$. Its mass spectrum gave the molecular ion peak at m/e 486 ($C_{33}H_{46}N_2O$). The examination of the i.r. spectrum of this compound revealed the absence of absorption bands at 1725 and 1230 cm^{-1} typical of acetate group[107] ($CH_3-\overset{O}{\overset{\|}{C}}-O-$). The absence of these characteristic bands in its i.r. spectrum completely ruled out the possibility of the expected compound (CCCXXXII). However, the presence of two nitrogen atoms in the molecule indicated the formation of pyrazole moiety. The sharp band at 1680 cm^{-1} clearly indicated the presence of an α,β-unsaturated carbonyl group in the molecule. Further, there were prominent absorption bands at 1600, 750 and 690 cm^{-1}, characteristic of monosubstituted benzene ring observed in phenylpyrazoline type derivatives.[102] The other significant band was observed at 1490 cm^{-1}, characteristic of >C=N vibrations.[107,120] The mass spectrum showed the molecular ion peak at m/e 486. These spectral data and molecular composition of the compound, m.p. 226° are compatible with the two isomeric structures (CCCXXX) and (CCCXXXI) formulated for this compound, discarding the expected structure (CCCXXXII).

The n.m.r. spectrum of this compound showed no signals in the region of vinylic (δ4-6.5) and acetate methyl protons (δ1.9-2.03) which supported the structures (CCCXXX) and (CCCXXXI). A broad multiplet centred at δ 7.5 integrating for 5 protons can be assigned to aromatic protons. The signals at δ 2.3 and 2.75 as multiplet are ascribable[106] to C_2-H_2 and C_7-H_2 (4 protons). The methyl protons were observed at δ1.3 (C_{10}-Me), 1.1, 0.8, 0.73 and 0.06. The n.m.r. data could also not help much in making a clear distinction between the two possible structures (CCCXXX) and (CCCXXXI). However, the structure (CCCXXX) is preferred over (CCCXXXI) for the compound, m.p. 236° on the basis of mechanistic and general considerations.

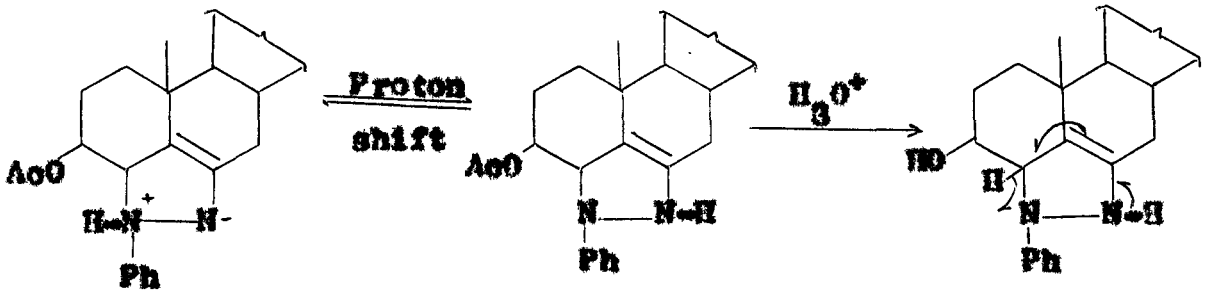
The formation of compound (CCCXXX) can be shown according to the proposed Scheme - 2(A and B). It may be noted that the carbonyl group at C_3 may be derived at any stage in the course of reaction from the acetate function. This finds support from the fact that the same compound (CCCXXX) was also obtained when the diketone (XCII) was subjected to the similar reaction conditions which will be described later on. The choice for the structure (CCCXXX) is dependent upon the fact that a five membered pyrazole ring is likely to be more stable than a four membered ring as in the proposed structure (CCCXXXI).

Scheme - 2

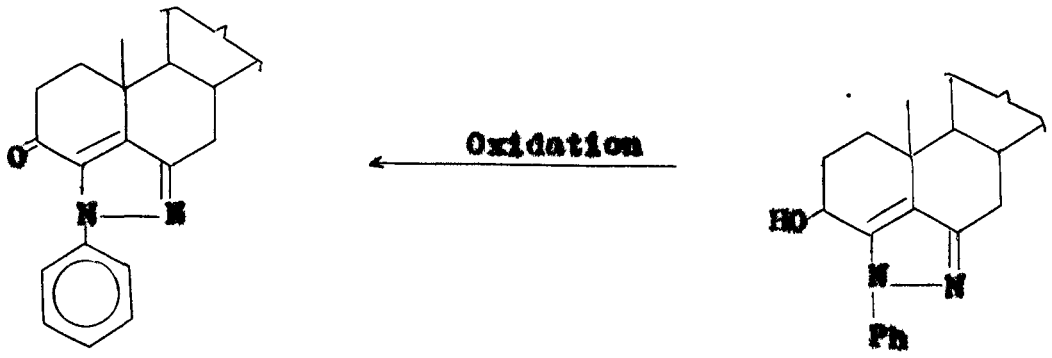
A.



(LXXXVI)



Aerial oxidation



Oxidation

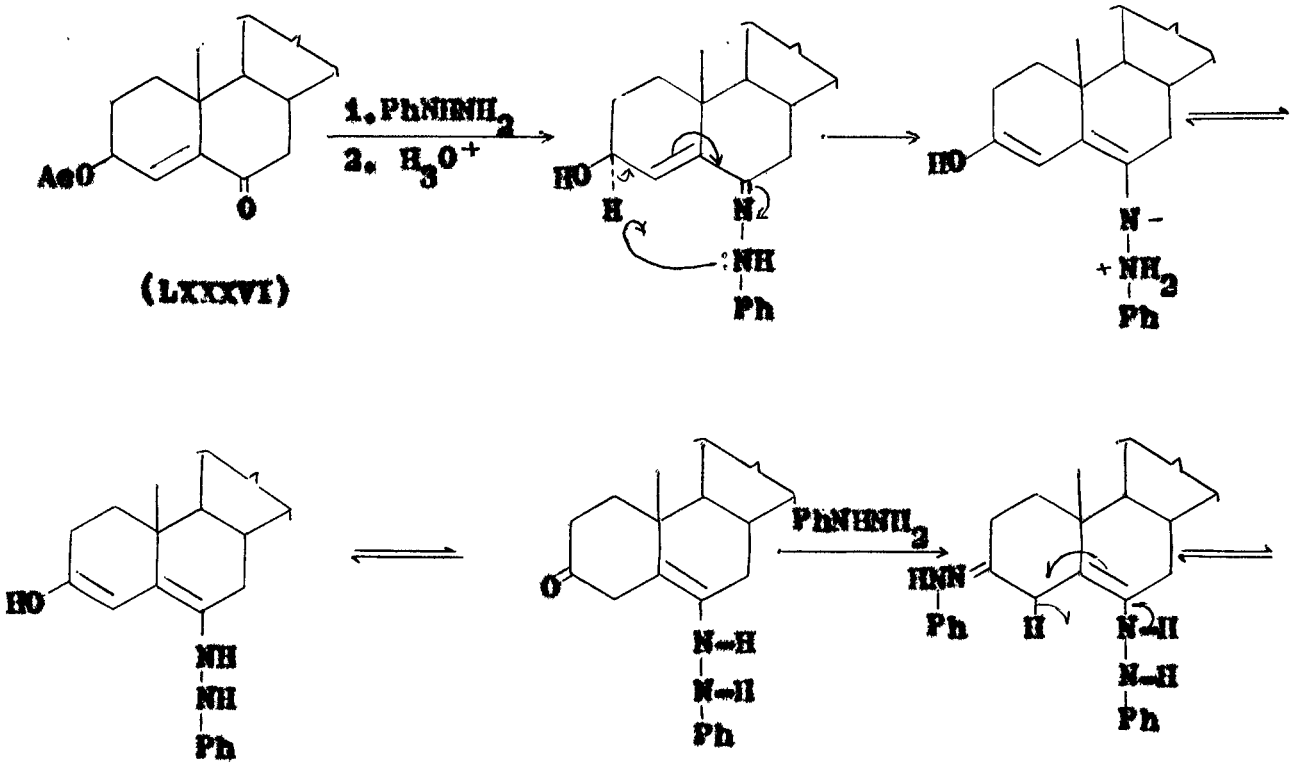
(CCCXXX-a)

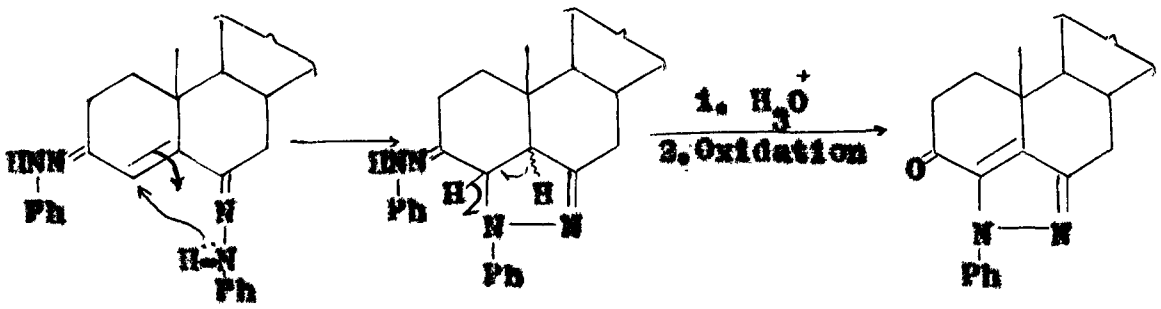
(CCCXXX)

In this mechanism, it is proposed that the aerial oxidation involving a free radical mechanism leads to the formation of the compound (CCCXXX). It receives further support from the observations[121-123] that in the oxidation of phenylhydrazone derivatives coupling of pseudo-allylic radical takes place following free radical mechanism. The hydroxyl intermediate (CCCXXX-a) being an allylic alcohol may undergo ready oxidation leading to an α,β-unsaturated ketone (more stable) system as in the end product. An alternative mechanism may also be suggested for the formation of (CCCXXX) from (LXXXVI) as shown in the Scheme - 2(B).

Scheme - 2

B.



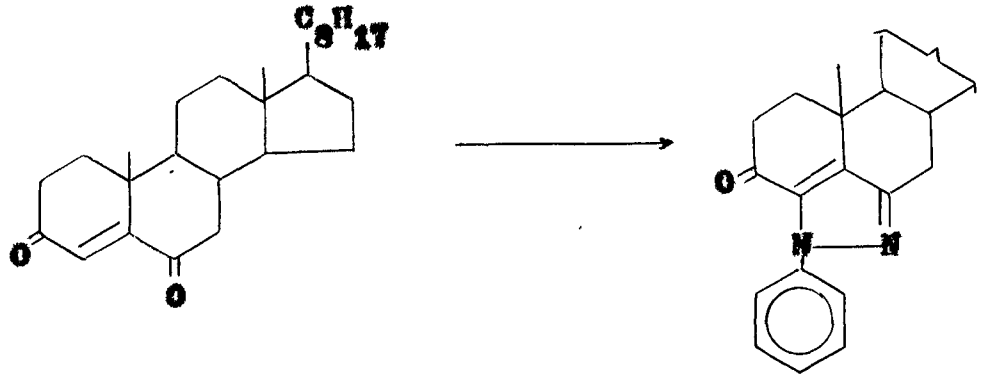


(CCCXXX-b) (CCCXXX-c) (CCCXXY)

In this mechanistic speculation, the intermediate compounds (CCCXXX-b,c) may presumably lead to the formation of desired compound (CCCXXY) through bishydrazone formation followed by condensation, hydrolysis and aerial oxidation, respectively. However, the intermediates (CCCXXX-b,c) were not isolated.

Thus the compound, m.p. 236° on the basis of its molecular composition, spectral evidences, mechanistic speculations and general consideration could best be characterised as cholest-3-oxo-4-eno [4,6-d]-2'-phenylpyrazole (CCCXXX).

<u>Reaction of cholest-4-ene-3,6-dione (XCII) with phenylhydrazine: Cholest-3-oxo-4-eno [4,6-d]-2'-phenylpyrazole (CCCXXX)</u>

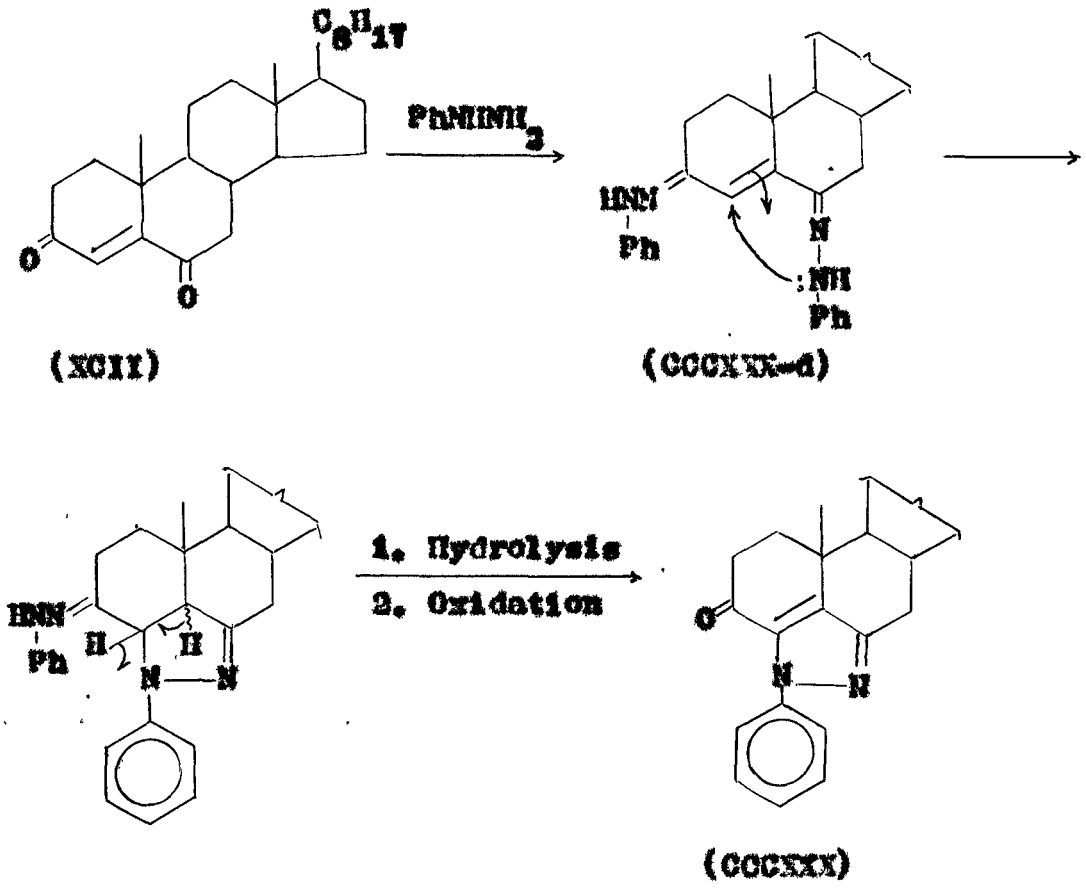


(XCII) (CCCXXX)

The formation of (CCCXXX) from the ketone (LXXXVI) was quite unexpected. Though a structure and probable course of mechanism has already been proposed for the compound, m.p. 336° as (CCCXXX), it was considered desirable to pursue this programme a little further. It was conceived that such a structure could be built from a diketone such as (XCII) which has two carbonyls at desirable positions. With this motivation, the diketone (XCII) was subjected to phenylhydrazine reaction. After usual work up and column chromatography, the compound, m.p. 236° was obtained as the sole product of the reaction. This compound was found to be identical with the pyrazole (CCCXXX), m.p. 226° obtained from (LXXXVI) in all respects (t.l.c., m.p., m.m.p., i.r., n.m.r. and mass). This then supports the view expressed earlier that the 3β-acetate function of (LXXXVI) is hydrolysed followed by oxidation to 3-keto function to give the pyrazole (CCCXXX). It is reasonable to argue at this stage that phenylhydrazone formation involving 6-keto function is the first stage in the reaction of (LXXXVI) and the generation of 3-keto function is a happening of subsequent steps during which time, it is expected that pyrazole ring formation has already taken place.

The formation of the compound (CCCXXX) from the ketone (XCII) may be shown according to the proposed Scheme - 3.

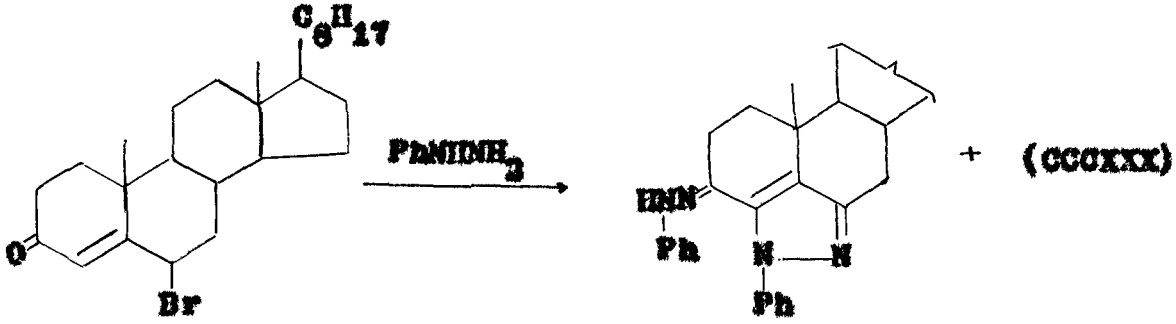
Scheme - 3



(XCII) (CCCXXX-d) (CCCXXX)

Reaction of 6β-bromocholest-4-en-3-one (LXXVI) with phenylhydrazine

The ketone (LXXVI) on treatment with phenylhydrazine in the presence of acetic acid under similar reaction conditions described above furnished after usual work up and column chromatography, two compounds, m.ps. 226° and 195°. Both the compounds obtained from this reaction showed negative Beilstein test.



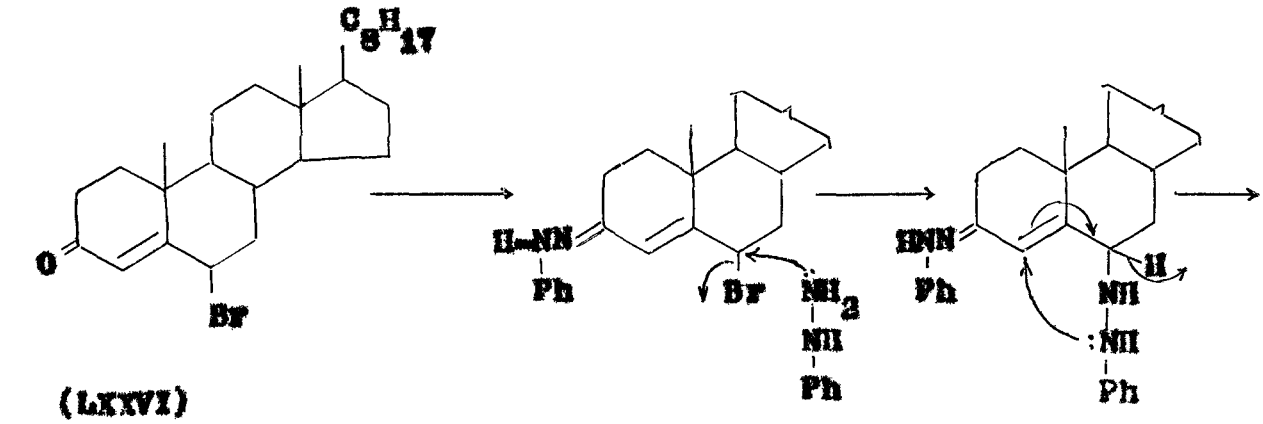
(LXXVI) (CCCXXXIII)

(CCCXXXIV) (CCCXXXV)

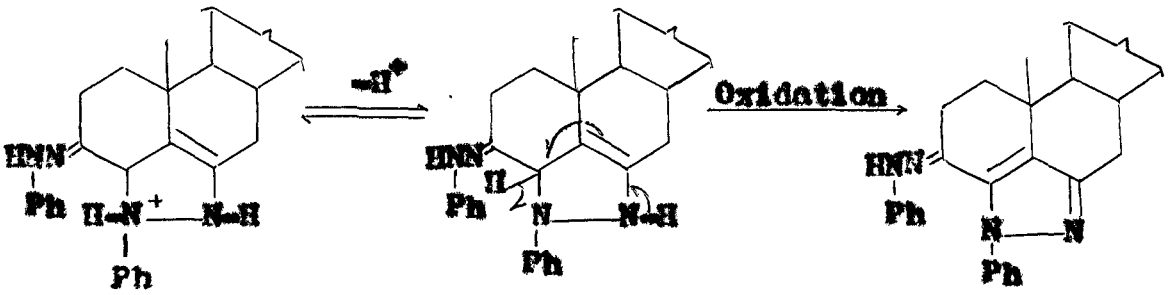
Interestingly, the reaction of the bromoketone (LXXVI) with phenylhydrazine too furnished, as one of its products, the same compound, m.p. 226° (identical in all respects) as obtained from the reaction of the ketones (LXXXVI) and (XCII). It again offered room for mechanistic considerations. The formation of the compound (CCCXXX) from (LXXVI) may be proposed according to Scheme - 4(A).

Scheme - 4

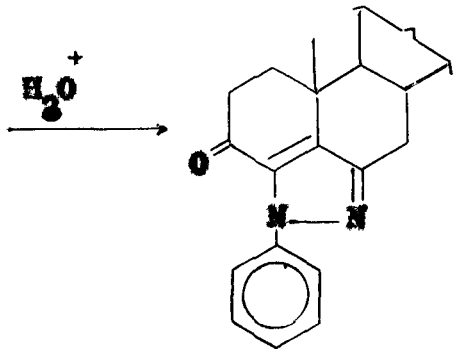
A.



(LXXVI)



(CCCXXXIII)



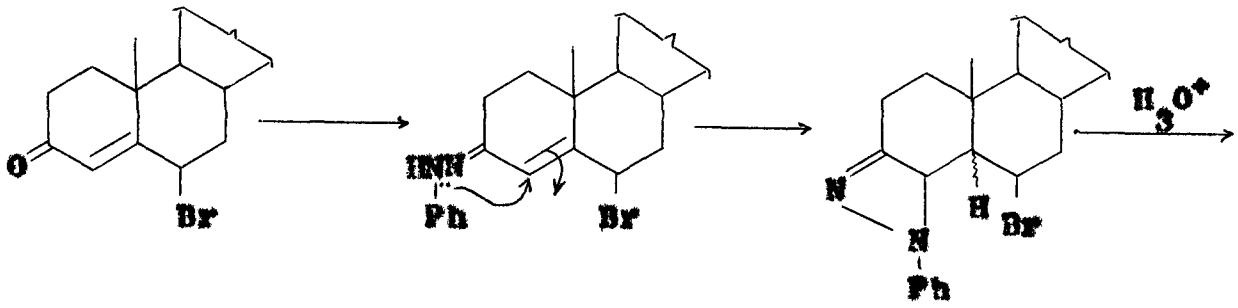
(CCCXXX)

In this scheme, as suggested in the previous mechanism, at first stage the formation of phenylhydrazone takes place. After this, the other molecule of phenylhydrazine attacks at C-6 in the fashion of nucleophilic displacement and thus bromide ion is liberated. Intramolecular reaction and oxidation results in the formation of the pyrazole (CCCXXX).

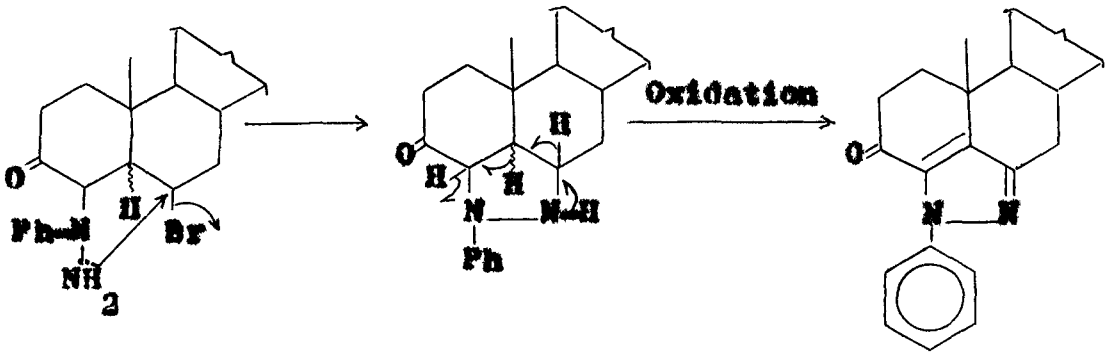
Alternatively, the following mechanism could also be taken into account to support the structure (CCCXXX) as proposed according to Scheme - 4(B).

Scheme - 4

B.

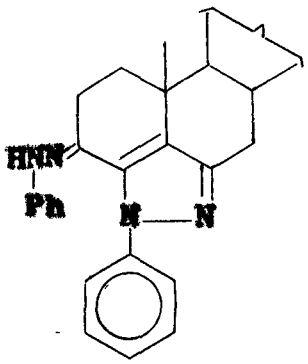


(LXXVI)

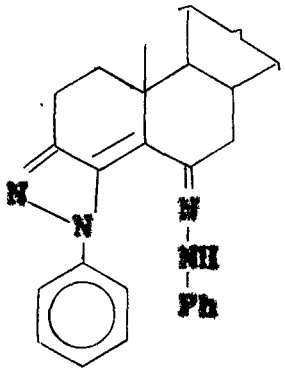


(CCCXXX)

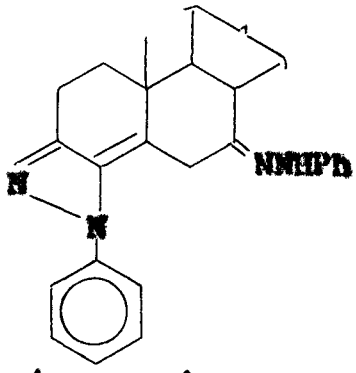
Characterisation of the compound, m.p. 195° as cholest-4-eno [4,6-d]-3'-phenylpyrazole-3-one phenylhydrazone (CCCXXXIII)



(CCCXXXIII)



(CCCXXXIV)



(CCCXXXV)

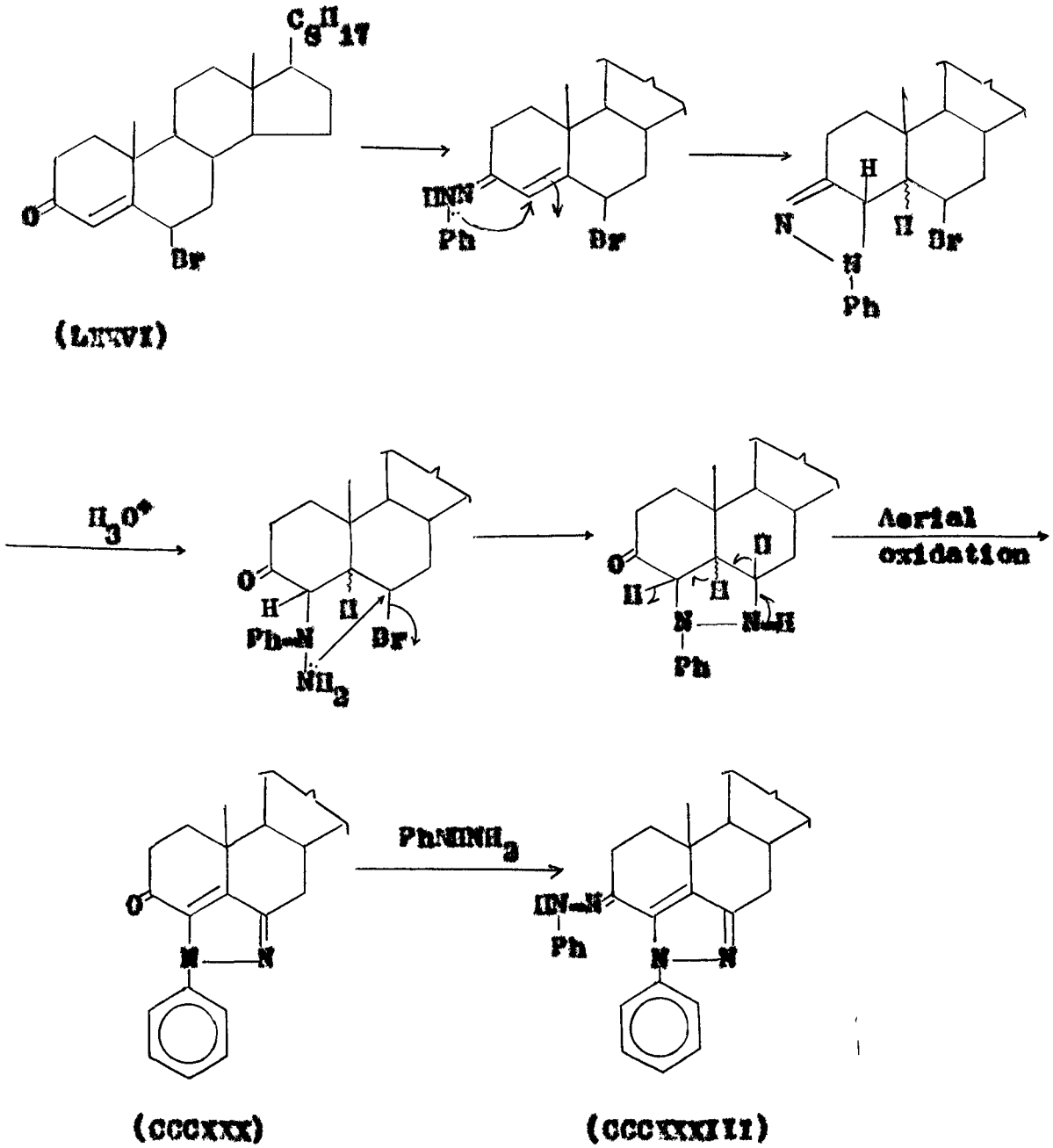
The compound, m.p. 195° analysed for $C_{39}H_{52}N_4$. This composition was further supported by its mass spectrum giving molecular ion peak at m/z 576 ($C_{39}H_{52}N_4$). The composition $C_{39}H_{52}N_4$ can lead to several possible structures (CCCXXXIII - CCCXXXV) formulated for the compound, m.p. 195° showing negative Bielstein test (Br absent).

The examination of the i.r. spectrum of the compound, m.p. 195° contrary to the first product of this reaction, revealed no absorption bands for the carbonyl group. The band observed at 3240 cm^{-1} can be ascribed to N-H vibration[107] which indicated the presence of phenylhydrazone moiety as shown in all the three possible structures (CCCXXXIII - CCCXXXV).

The bands of 1603, 750 and 695 cm^{-1} could be attributed to the aromatic grouping .[103,107] Two prominent absorption bands at 1590 and 1490 cm^{-1} are assigned to >C=N- vibrations. These i.r. data are in agreement with the three proposed structures (CCCXXXIII - CCCXXXV). A distinction between the structures (CCCXXXIII - CCCXXXIV) could be made on the basis of its n.m.r. spectrum. The n.m.r. spectrum of the compound, m.p. 195° exhibited a signal between δ 7.1 - 7.5 as multiplet integrating for ten protons (2 C_6H_5). A singlet at δ 13.7 may be ascribed to N-H proton of the phenylhydrazone moiety present in the molecule. This downfield shift of N-H proton to such an extent is attributable to the fact that there is no vicinal coupling and this receives support from the earlier observations.[124,125] The other notable features of the spectrum were found to show signals at δ 2.9 and 2.35. The multiplet at δ 2.9 may be ascribed to C_2-H_2 and the doublet at δ 2.35 (J 10 Hz) to C_7-methylene protons. Methyl protons were seen at δ 1.2, 0.9, 0.8 and 0.73. The structure (CCCXXXV) can be discarded on the basis of n.m.r. spectrum where a singlet would have appeared in the region δ 3.6-3.9 for C_6-methylene protons and one more singlet was expected in the region of δ2.4-2.6 for C_8-β-H.[106] Now the choice is narrowed down between the two possible structures (CCCXXXIII) and (CCCXXXIV) because the i.r. and n.m.r. values are in good agreement with

these two structures. Mechanism wise both the structures (CCCXXXIII) and (CCCXXXIV) are possible. The formation of the structure (CCCXXXIII) from (LXXVI) can be shown according to Scheme-5.

Scheme- 5

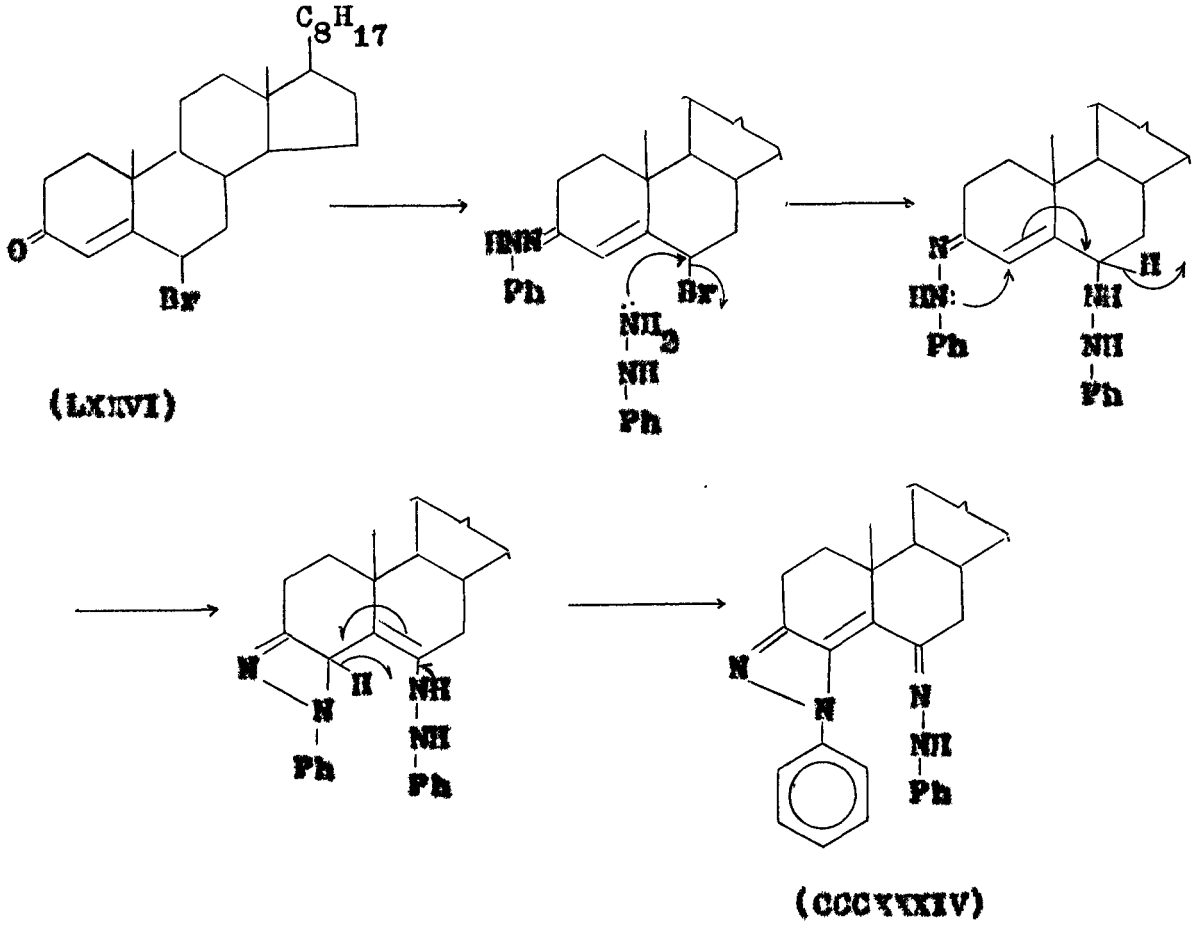


(LXXVI)

(CCCXXX) (CCCXXXIII)

Alternatively, the formation of the structure (CCCLXXXIV) from (LXXVI) can also be shown according to the proposed mechanistic path ways as shown in Scheme - 6.

Scheme - 6



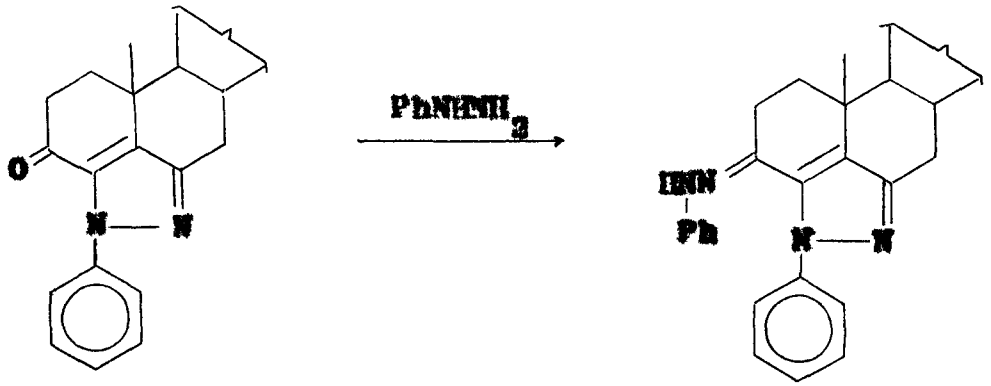
(CCCLXXXIV)

The compound (CCCLXX) which has been obtained from this reaction as one of the products, can conveniently lead to (CCCLXXIII) and vice-versa. It is reasonable to prefer the

structure (CCCXXXIII) over (CCCXXXIV) for the compound, m.p. 195° in the light of spectral data, mechanistic and general considerations with certain limitations. In view of this discussion, the compound, m.p. 195° can be characterised as cholest-4-eno [4,6-d]-2'-phenylpyrazole-3-one phenylhydrazone (CCCXXXIII).

Further, to substantiate the structure (CCCXXXIII), the compound (CCCXXX) was subjected to the reaction of phenylhydrazine under mild conditions.

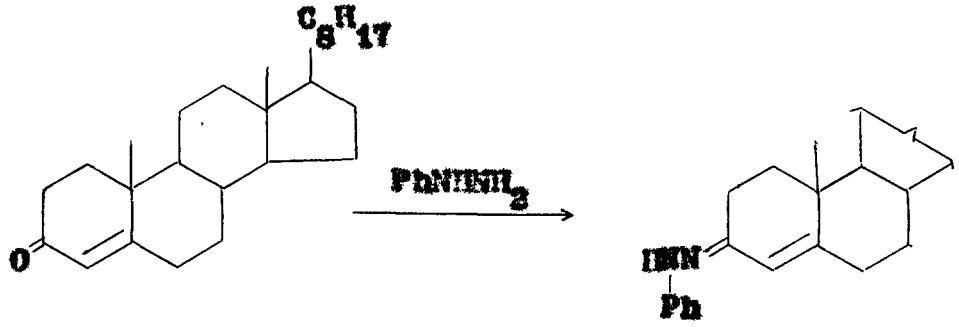
This reaction, after usual work up, afforded a compound, m.p. 195° which was found identical in all respects (t.l.c., m.p., m.m.p. and spectra) with the one obtained from the reaction of 6β-bromocholest-4-en-3-one (LXXVI) with phenylhydrazine as one of its products.



(CCCXXX) (CCCXXXIII)

This chemical transformation confirms the structure (CCCXXXIII) for the compound, m.p. 195° and thus the structure (CCCXXXIV) is disfavoured.

Reaction of cholest-4-en-3-one (LI) with phenylhydrazine: Cholest-4-en-3-one phenylhydrazone (CCCXXXVI)



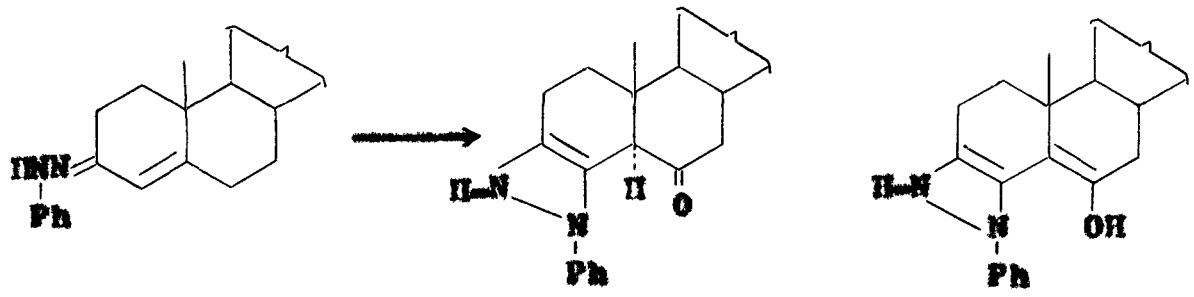
(LI) (CCCXXXVI)

The reaction of cholest-4-en-3-one (LI) with phenylhydrazine, using a few crystals of p-toluenesulphonic acid as catalyst, provided after work up a single compound, m.p. 144°.

The compound, m.p. 144°, analysed for $C_{33}H_{50}N_2$ and showed absorption bands in its i.r. spectrum at 3330-3420 br (-NH-Ph), 3030, 1600 sh (aromatic C-H), 1590 and 1495 cm^{-1} characteristic absorption for >C=N vibration.[107] It showed no band for the carbonyl group. The n.m.r. spectrum of this compound exhibited a broad multiplet at δ 7.2 integrating for five protons of aromatic group. No separate signal for N-H proton was observed. It can be mentioned that N-H proton may be considered to be buried in the aromatic proton multiplet.

as such cases have been reported earlier.[121,122] A singlet was observed at δ 6.3 which may be assigned to C_6-vinylic proton. A broad multiplet centred at δ 2.3 is attributed to C_3-methylene protons. Other signals were observed at δ 1.1 (C_{10}-CH_3), 0.72 (C_{13}-CH_3), 0.96, 0.83 and 0.78 (methyl groups). On the basis of these spectral values, the compound, m.p. 144° was characterised as cholest-4-en-3-one phenylhydrazone (CCCXXXVI).

Reaction of cholest-4-en-3-one phenylhydrazone (CCCXXXVI) with acetic acid under reflux

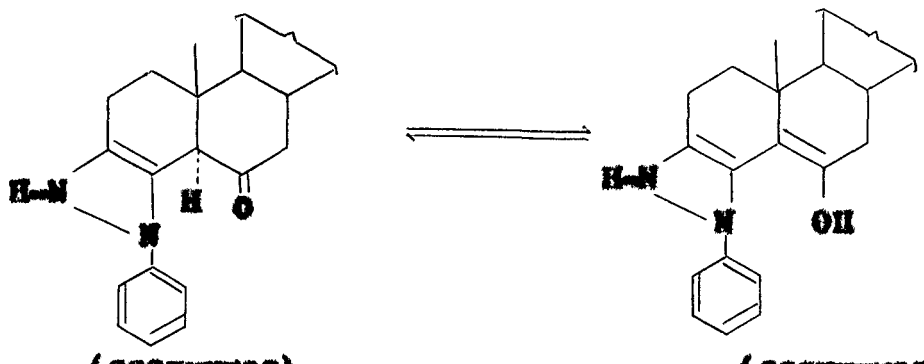


(CCCXXXVI) (CCCXXXVII) (CCCXXXVIII)

The phenylhydrazone (CCCXXXVI) was heated under reflux with glacial acetic acid for two hours and worked up in the usual manner. The column chromatography of the reaction mixture over silica gel afforded the compound, m.p. 185°.

This reaction was found to be at some variance to our expectation of the formation of a pyrazole ring system. The examination of spectral data of the compound obtained from this reaction revealed that doubly unsaturated five membered pyrazole moiety has not been formed as in the case of previous reactions under similar conditions. To our knowledge, pyrazoles from C_4-C_5 unsaturated steroids have not heretofore been reported. Though Δ^4-3 ketone moiety is a necessary requisition for such reactions, but since C_5- in such cases happens to be tetra-substituted, perhaps, prevents the formation of a pyrazole system. Thus besides an α,β-unsaturated carbonyl group, there should be one hydrogen atom at the carbon, β - to the keto function to facilitate the pyrazole formation. This left us to look at it otherwise and the characterization of the compound was considered in the light of its molecular composition and spectral values (i.r., n.m.r. and mass).

<u>Characterization of the compound, m.p. 185° as 5α-cholest-3-en-6-one [3,4]-N,N-phenylhydrazine (CCCXXXVII)</u>



(CCCXXXVII) (CCCXXXVIII)

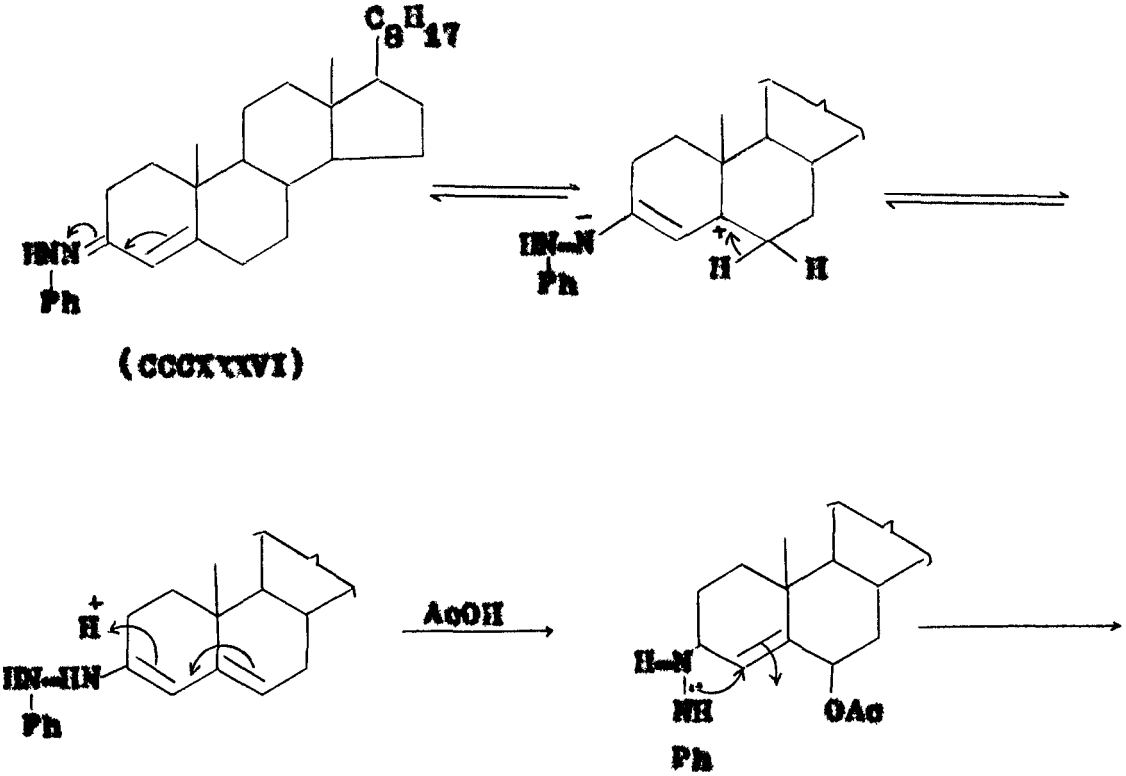
The compound, m.p. 185° analysed for $C_{33}H_{48}N_2O$. Its mass spectrum gave molecular ion peak at m/e 488 ($C_{33}H_{48}N_2O$). The molecular composition showed the presence of one oxygen atom indicating thereby that oxidation has taken place during the course of the reaction. The molecular composition and mass spectrum of the compound, m.p. 185° were found compatible with both the structures (CCCXXVII) and (CCCXXXVIII).

The i.r. spectrum of the compound, m.p. 185° gave a broad band at 3360 cm^{-1} which may be ascribed to C-N-H stretching. A sharp band at 1705 cm^{-1} is characteristic of an isolated carbonyl chromophore. This observation supports the presence of a keto function in the molecule. Other bands were found at 1650, 1530 and 1460 cm^{-1} ascribable to C=C-N-N- stretchings. These i.r. values revealed that the formation of a pyrazole has not taken place. The band at 3360 cm^{-1} signifies the presence of N-H vibration as in the proposed structure (CCCXXXVII). It finds ample support from the n.m.r. spectrum. The n.m.r. spectrum of this compound exhibited a broad singlet at δ 9.9 integrating for one proton ascribable[124] to N-H. A broad multiplet at δ 7.4 was observed for aromatic protons. A singlet at δ 3.7 integrating for one proton may be assigned to C_5-H. A doublet centred at δ2.67 (J 10 Hz) could be attributed to C_7-H_2. Other signals were observed at δ 1.3 (C_{10}-CH_3), 1.2, 0.9, 0.8 and 0.65 (methyl

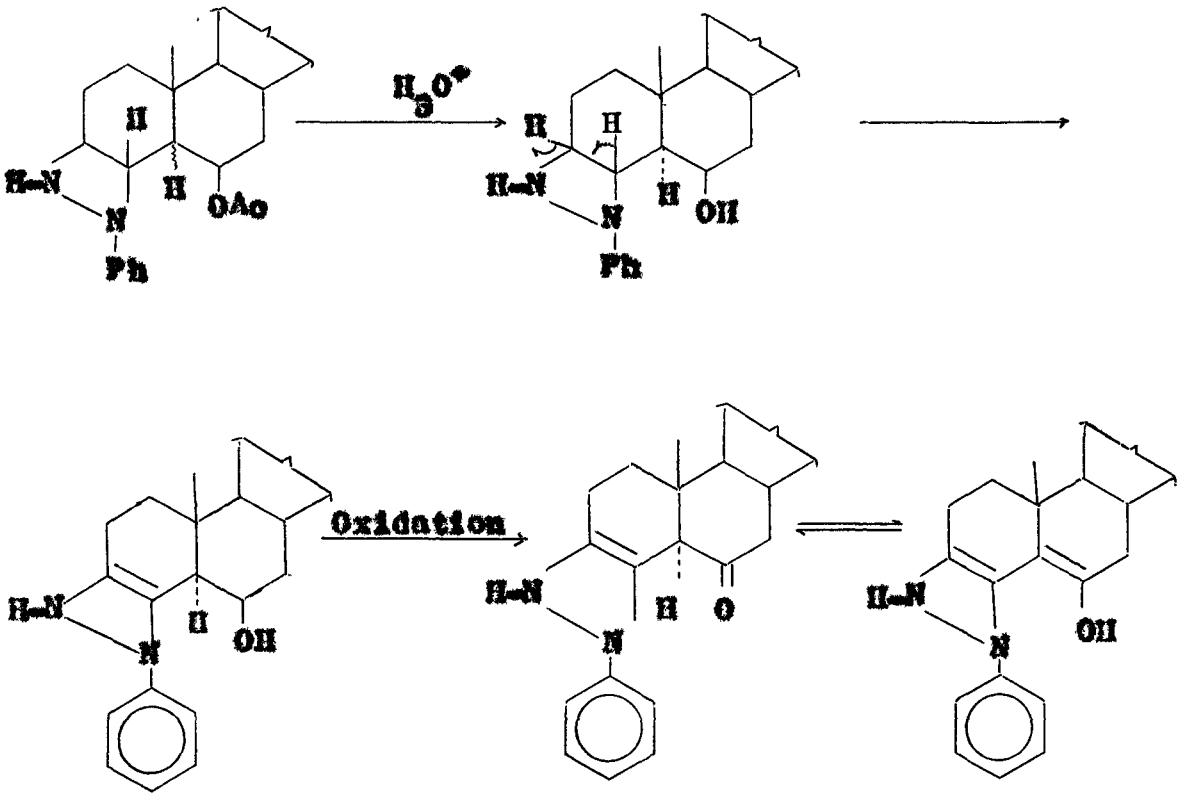
protons). The i.r. and n.m.r. spectra of the compound, m.p. 185° are in good agreement with the structure (CCCVXXVII). The presence of a weak broad band in its i.r. spectrum at 3400-3500 cm^{-1} suggests that the compound (CCCVXXVII) may be in equilibrium with its enolic structure (CCCXXXVIII). Thus on the basis of foregoing discussion and spectral properties, the compound, m.p. 185° could be characterized as 5α-cholest-3-en-6-one [3,4]-N,N-phenylhydrazine (CCCXXXVII).

The mechanism of formation of the compound, m.p. 185° from (CCCVXXVI) can be shown according to Scheme - 7.

Scheme - 7.



(CCCXXXVI)

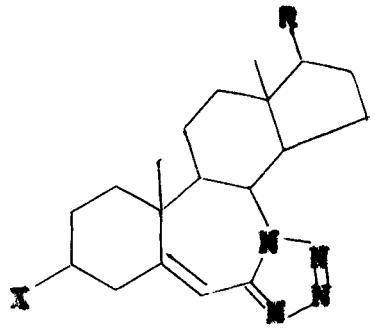


(CCCXXXVII) (CCCXXXVIII)

It can be mentioned that attempted reactions of cholest-3-en-7-one (CII), its 3β-acetoxy (CVIII) and 3β-chloro (CV) analogues with phenylhydrazine in the presence of acetic acid failed under similar reaction conditions described above.

Mass Spectrometry of Steroidal Tetrazoles

In recent past, the synthesis of a number of steroidal tetrazoles in the cholestane series has been reported.[59-64] A survey of literature reveals that little work on mass spectrometry of tetrazoles has been carried out.[120] This chapter is concerned with a detailed mass spectral study of 7a-aza-tetrazoles in the stigmastane series in view to substantiate the structures and derive some characteristic pattern of fragmentation peculiar for such compounds and to obtain information in support of our previous study on analogous 7a-azatetrazoles in the cholestane series. For this, the mass spectrometry of some of those tetrazoles namely, 7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXVIII), 3β-hydroxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXVI), 3β-acetoxy-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXIX), and 3β-chloro-7a-aza-B-homostigmast-5-eno [7a,7-d] tetrazole (CCCXX) along with their 3β-substituted analogous tetrazoles (CLXXXI, CLXXX and CXLI), in the cholestane series have been undertaken.



	X	R
(CCCXVIII)	H	$C_{10}H_{21}$
(CCCXXI)	OH	$C_{10}H_{21}$
(CCCXIX)	OAc	$C_{10}H_{21}$
(CCCXX)	Cl	$C_{10}H_{21}$
(CLXXXI)	OH	C_8H_{17}
(CLXXX)	OAc	C_8H_{17}
(CXLI)	Cl	C_8H_{17}

These compounds are structurally very close to each other and it was anticipated that they will follow similar pattern of fragmentation thus offering a means of their characterization by mass spectrometry as observed in the case of 7a-aza-lactams.[127] However, all the expectations were not fully realised as the substituents at C_3 influenced the fragmentation in no uncertain terms.

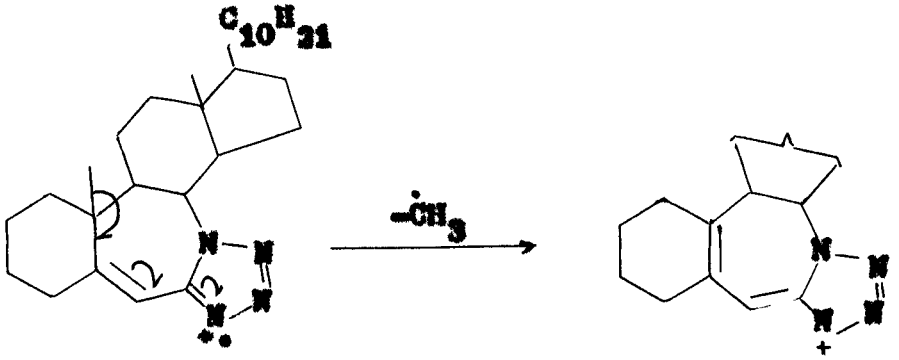
It has been noted that all the spectra of 3β-substituted 7a-azatetranoles, both in the stigmastane as well as cholestane series are conspicuous by the presence of a common fragment ion peak at m/e 175 which may be considered to be of diagnostic

value in the characterization of such structurally related compounds. In the absence of a substituent at C_3 as in (CCCXVIII), the peak corresponding to the common ion was noted at m/z 177.

The mass spectrum of 7a-nor-B-homostigmast-5-ene [7a,7-d] tetrazole (CCCXVIII) (Fig. 1) gave molecular ion peak at m/z 452 ($C_{29}H_{48}N_4$) followed by other salient fragment ion peaks at m/z 437, 409, 177, 149, 135 and lower mass peaks. The formation of some of the relevant fragment ions has been explained in the schemes given below.

<u>m/z 437</u>

This fragment ion can be obtained by the loss of a methyl group from the molecular ion (CCCXVIII'); the greater contribution may be expected from the loss of C_{10}-CH_3 as this is allylic to C_5-C_6 double bond.



(CCCXVIII') m/z 437

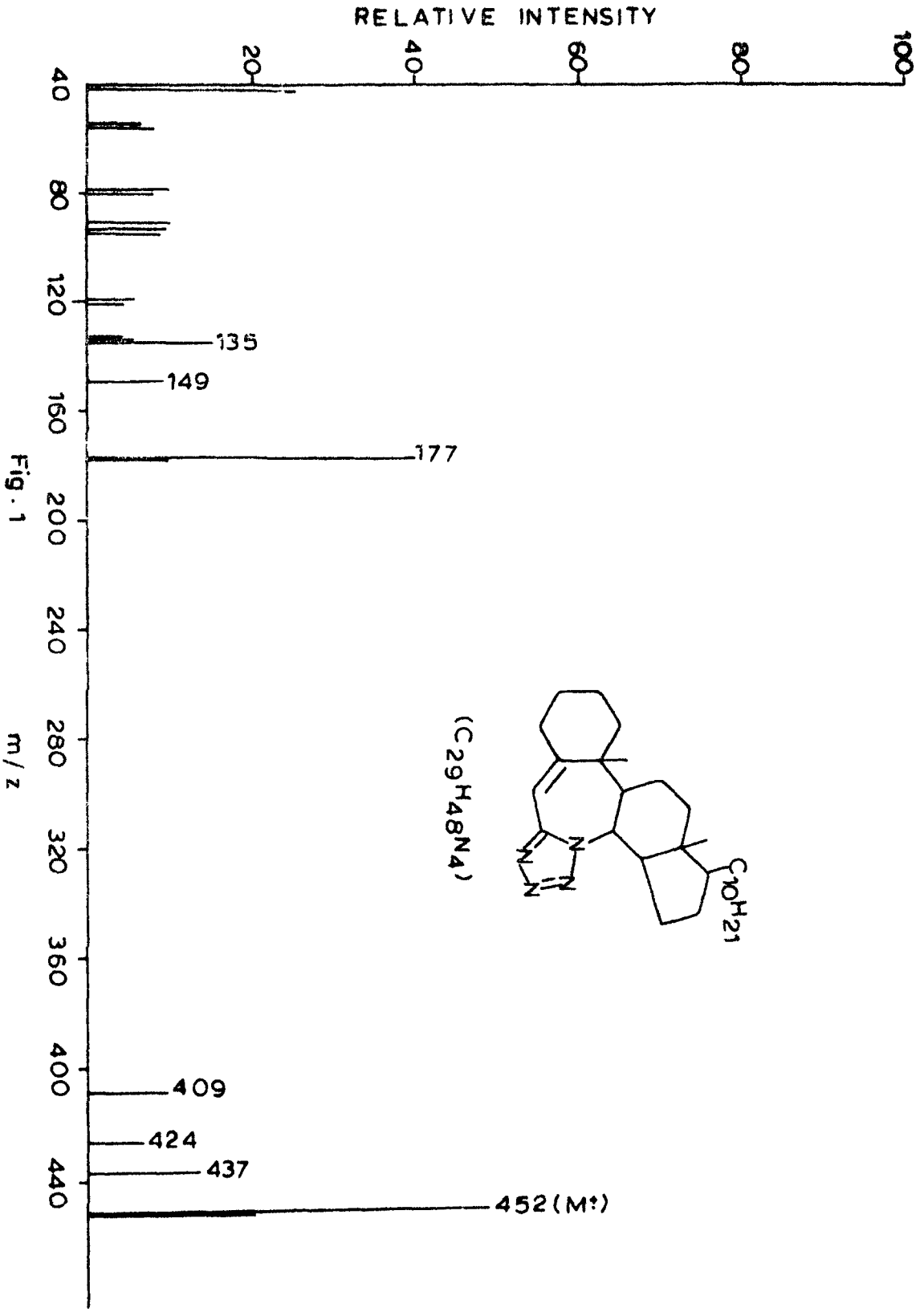
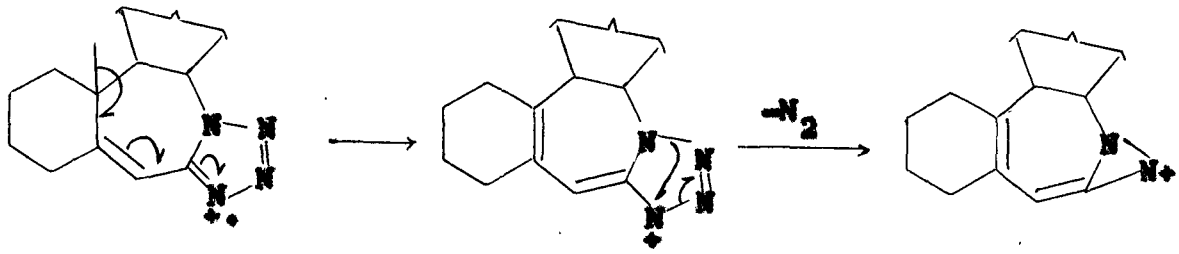

RELATIVE INTENSITY
20
40
60
80
100
40
80
120
135
149
160
177
200
240
280
320
360
400
409
424
437
440
452(M+)
m/z
(C29H48N4)
C10H21

Fig. 1

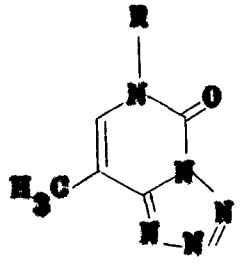
m/z 409

This important ion results by the total loss of mass unit 43 from the molecular ion. The mass unit 43 can be conveniently obtained by a combination of N_2 and CH_3 units. Therefore, it may occur either by the total loss of mass unit 43 ($M-CH_3-N_2$) or directly from the ion m/z 437 by the loss of N_2.

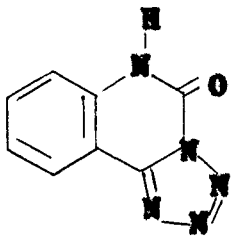


(CCCXVIII') m/z 437 m/z 409

It is pertinent to mention here that the loss of N_2 from tetrazole moiety is well documented[126] where it takes preference over the loss of CO (mass unit 28) in molecules of the tetrazoles type given below.



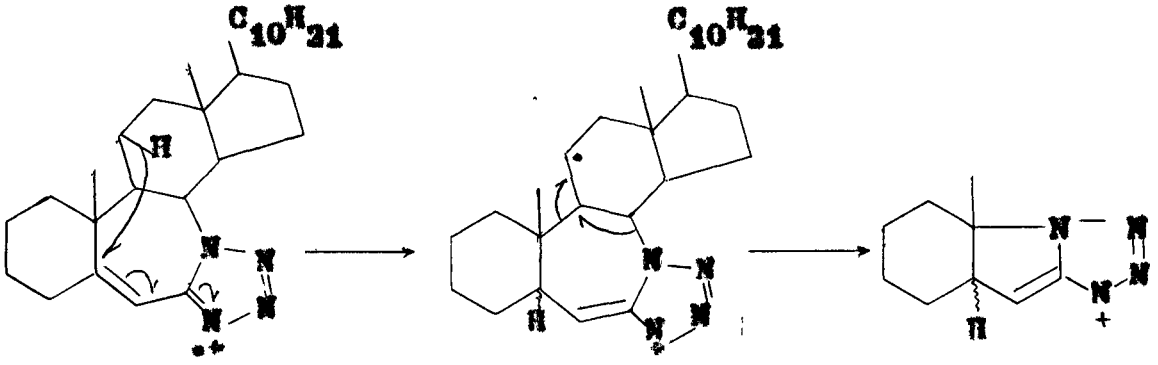
(CCCXLI) R, H
(CCCXLII) R, CH_3



(CCCXLIII)

m/s 177

The spectrum of this compound is devoid of any mid-range fragment ion peaks between m/s 400 and m/s 177 and it appears that hydrocarbon moiety hardly triggers the fragmentation in this case. The genesis of this important fragment ion with composition $C_9H_{13}N_4$, comparable with the common ion m/s 175 observed in all the 3β-substituted anabolic tetrazoles, can be rationalised according to the mechanism given below.

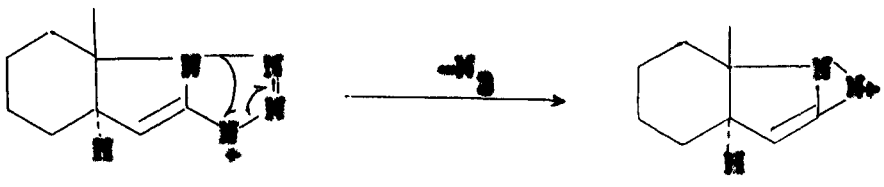


(CCCXVIII')

m/s 177
($C_9H_{13}N_4$)

m/s 149

This fragment ion may be obtained by the loss of N_2 from the ion m/s 177.



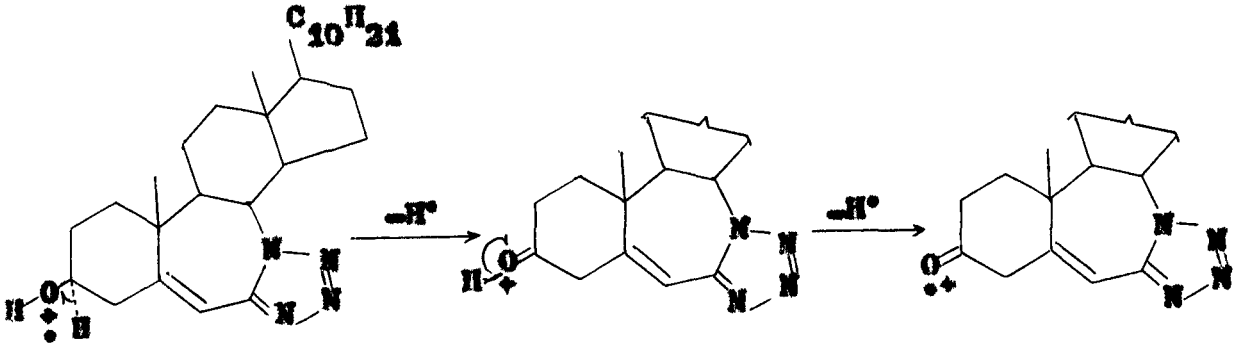
m/s 177

m/s 149

The mass spectrum of 3β-hydroxy-7a-aza-B-homoetiocast-5-ene [7a,7-d] tetrazole (CCCXXI) (Fig. 2) gave the molecular ion peak at m/z 468 (base peak; $C_{29}H_{48}N_4O$) followed by other significant fragment ions at m/z 466, 453, 450, 435, 432, 412, 411, 193, 175, 147, 135 and lower mass peaks. The mode of formation of some of the relevant ions has been rationalised in the following schemes.

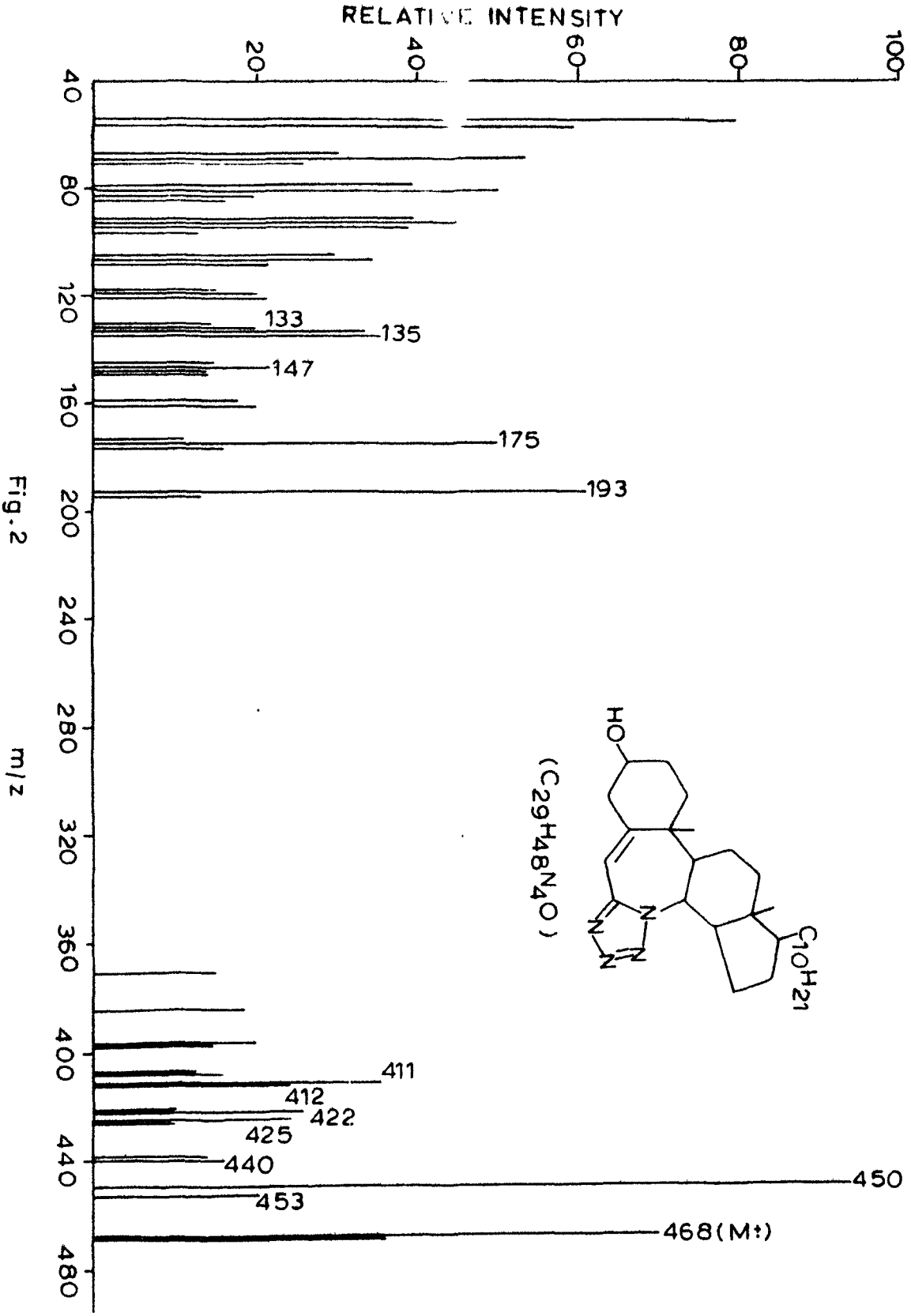
m/z 466

This fragment ion obviously results by the successive loss of hydrogens from the molecular ion and are of common occurrence in the spectra of 1° and 3° alcohols.[139]



(CCCXXI')
$M^{+\cdot}$ 468

m/z 466


RELATIVE INTENSITY
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160
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320
360
400
440
480
m/z
133
135
147
175
193
411
412
422
425
440
450
453
468(M+)
HO
(C29H48N4O)
C10H21

Fig. 2

m/e 452

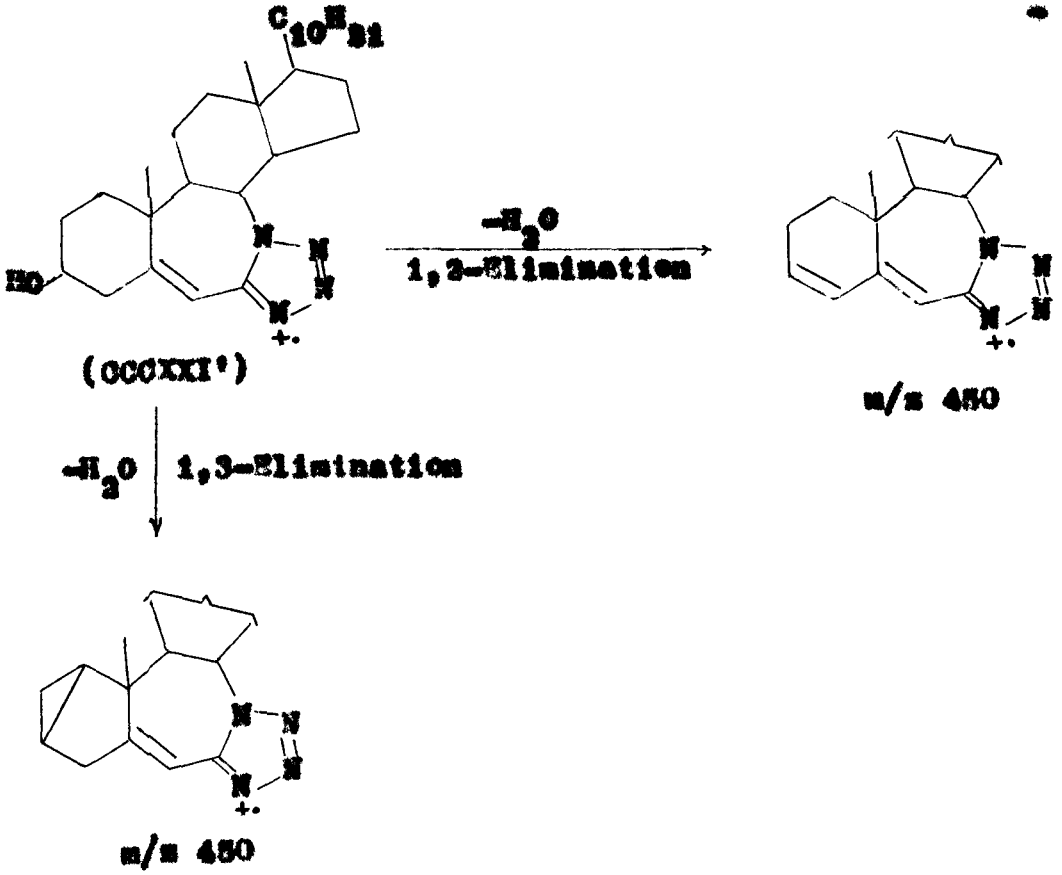
This ion can be obtained by the loss of one of the methyl groups of (CCCXXI'); again the loss of C_{10}-CH_3 is more likely than C_{12}-CH_3.

m/e 451

The ion m/e 451 results by the loss of a methyl group from the fragment ion m/e 466. In this case also the loss of C_{10}-CH_3 is likely to be dominant.

m/e 450

This significant fragment ion may be conveniently obtained by the loss of a molecule of water from the molecular ion. The loss of water molecule in alcohols under electron-impact usually involves, 1,3 and 1,4-eliminations. However, there is no possibility of the latter situation. It is also possible that due to the presence of double bond, the loss of water molecule may involve 1,2-elimination as to give a more stable conjugated diene system.

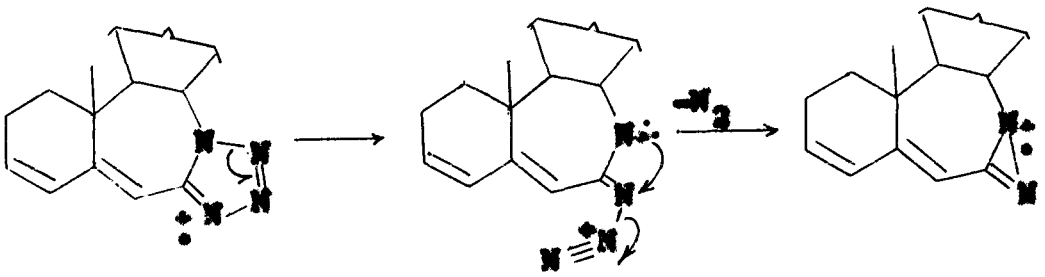


m/z 425

This fragment ion results by the total loss of mass unit 43 from the molecular ion. The mass unit 43 can be conveniently obtained by a combination of CH_3 and N_2 units. The loss of CH_3 and N_2 from the molecular ion can be rationalised as shown in the previous example (CCCXXIII).

m/z 422

This fragment ion can be shown to arise by the loss of N_2 from the ion m/z 450.

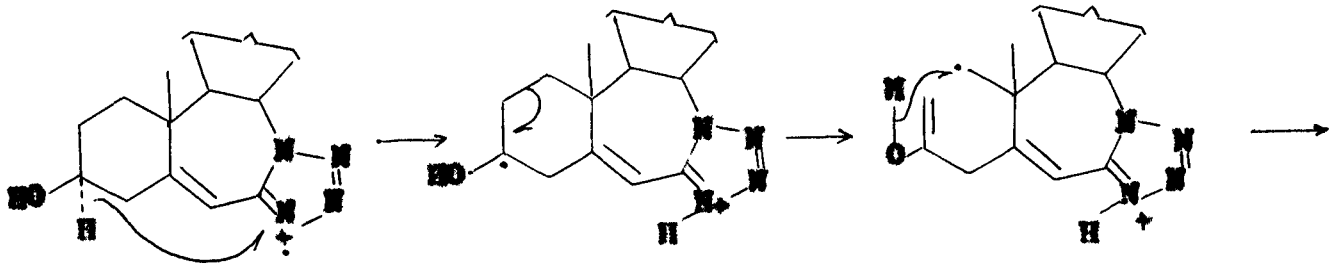


m/z 450 m/z 421

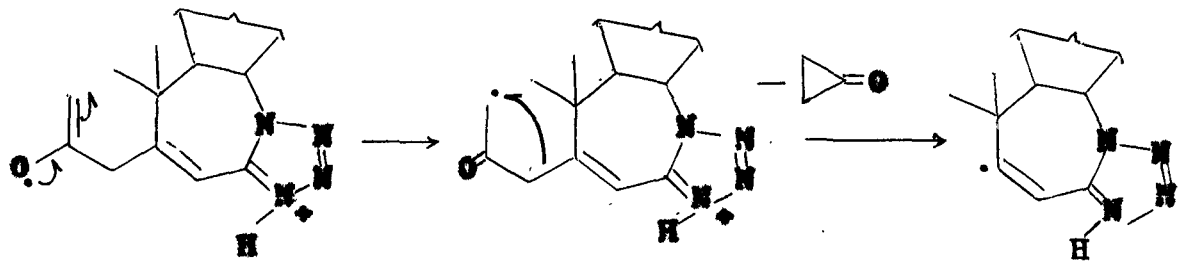
m/z 412

The fragment ion m/z 412 (M-56) at the first sight appeared to be the result of the loss of all nitrogen (4N) from the molecular ion (CCCXXI'). However, there was no evidence of M-56 ion in the spectra of other tetrazoles under the present study. A few mechanistic speculations have been suggested for the genesis of the ion m/z 412.

(1) Loss of $\begin{matrix} CH_2 \\ CH_2 \end{matrix}$ C=O moiety from the molecular ion.



(CCCXXI')

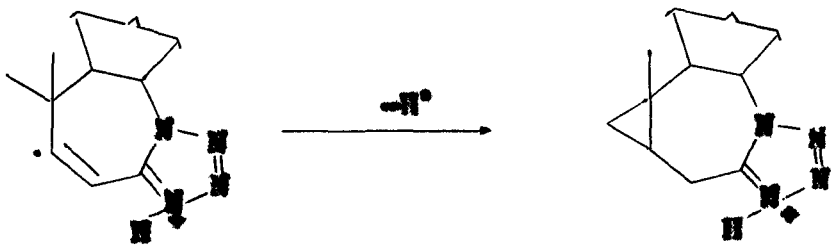


m/z 412

It is reasonable to mention here that the 3β-hydroxy derivatives (CCCXXI) and (CLXXXI) are similar to each other to a considerable extent regarding the fragment ions particularly m/z 412/411 and m/z 384/383 from them, respectively. Such fragmentations were not observed in any of the 3β-acetoxy or 3β-chloro derivatives (CCCXIX) and (CLXXX) or (CCCXX) and (CXLI). This observation supports the statement that the hydroxy function has specific role in the fragmentation.

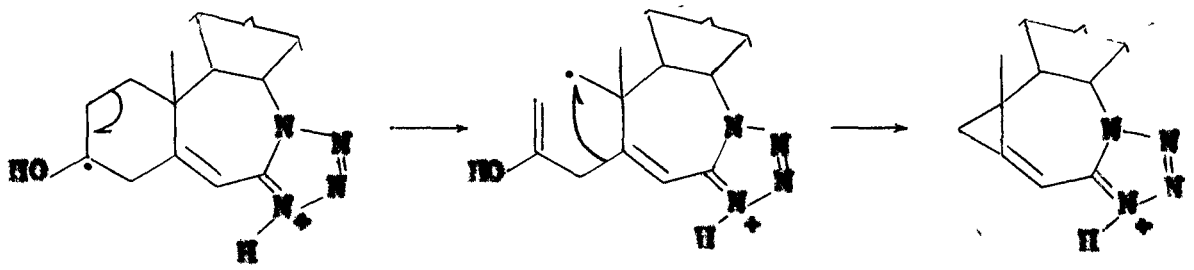
<u>m/z 411</u>

The ion m/z 411 can arise by the loss of 1 hydrogen from the ion m/z 412.



m/z 412 m/z 411

The fragment ion m/z 411 can also be obtained directly from the molecular ion by the loss of mass unit 57 as suggested in the scheme below.

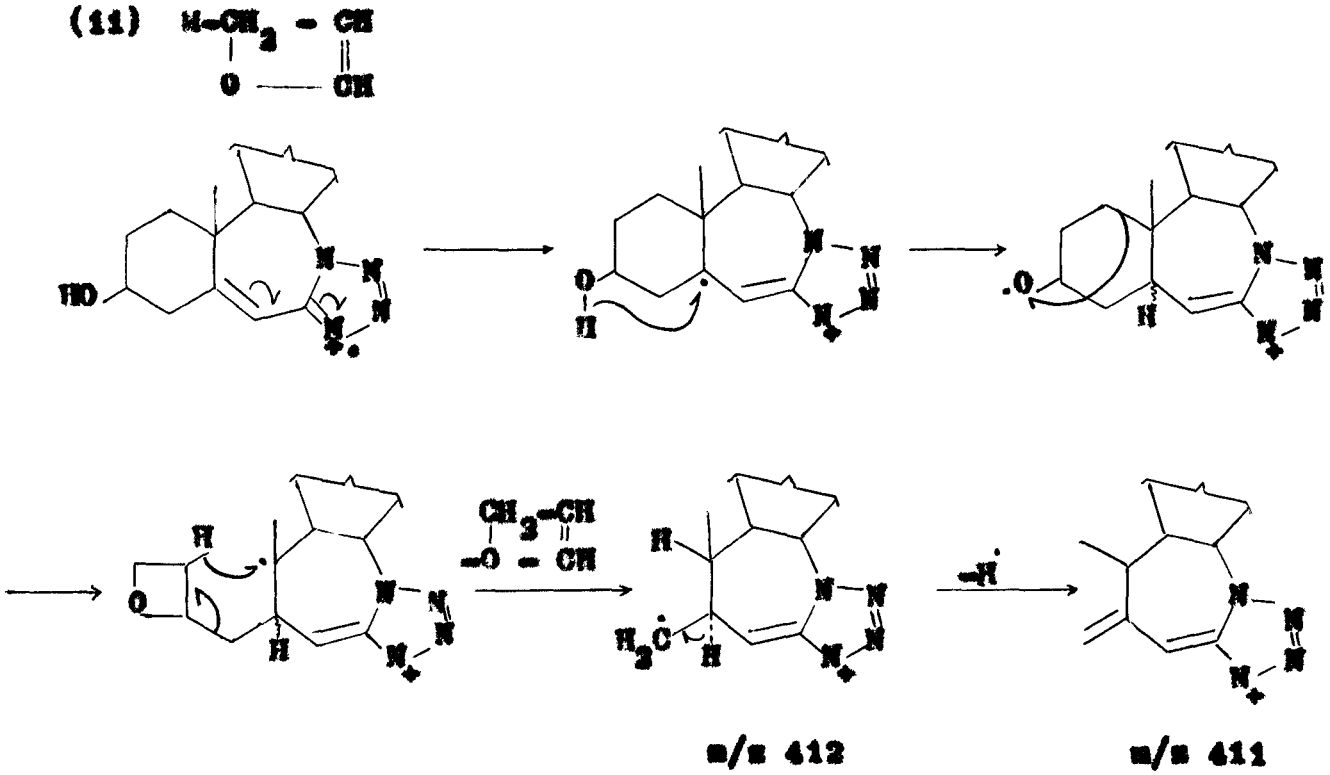


m/z 411

The ion m/z 411, according to the above approach should be possible also for the other tetrazoles (CCCXIX) and (CCCXX), but in none of them the ion m/z 411 was obtained. Further, the ion m/z 413 is recorded only in the case of 3β-hydroxy derivative (CCCXXI). This in case presumably leads to the formation of the ion m/z 411 by the loss of 1 hydrogen.

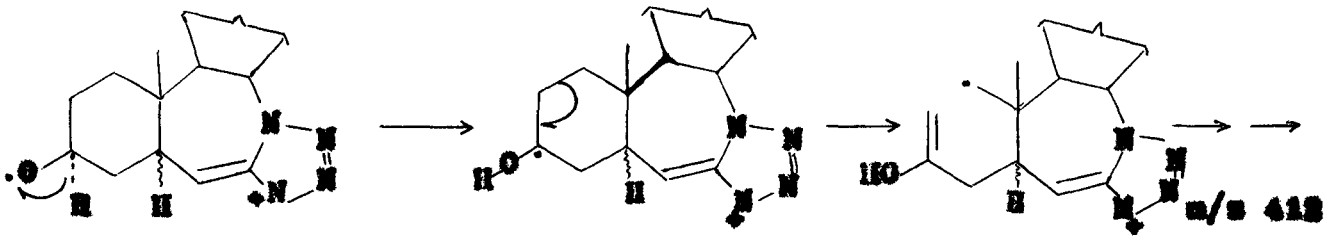
The formation of these two important fragment ions m/z 413 and m/z 411, probably depends upon the presence of the moiety H-O-C- in the molecule and hence these two fragments are noted in the case of (CCCXXI) only. Their formation may also be shown by other alternative pathways given below.

(11)



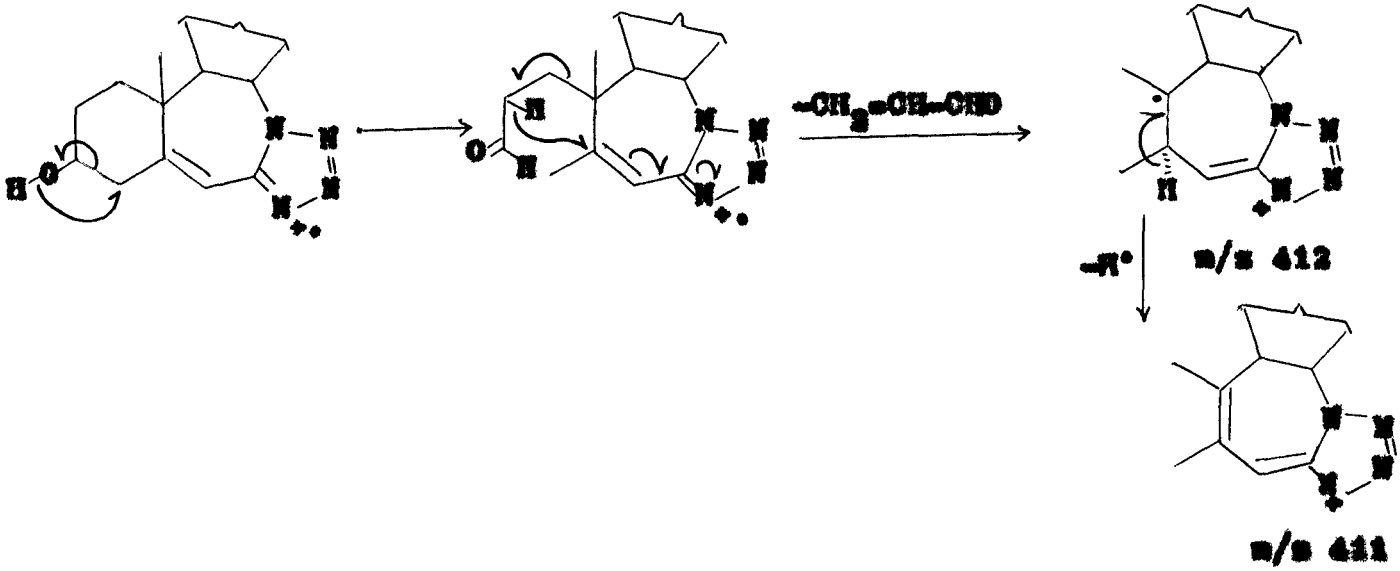
m/z 412 m/z 411

(111)



m/z 412

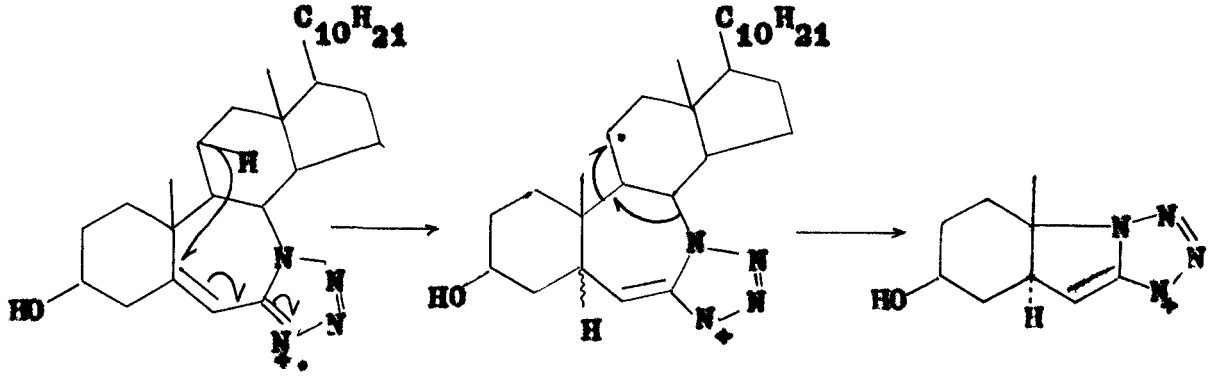
(1v)



m/z 412 m/z 411

m/z 193

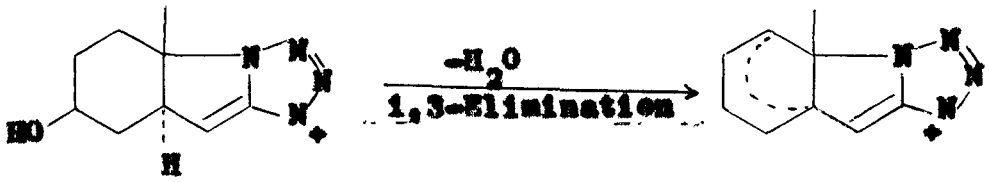
Interestingly, there is no fragment ion peaks between m/z 411 and m/z 193 and it appears that hydrocarbon moiety hardly triggers the fragmentation in this case. The formation of the ion m/z 193 can be rationalised according to the mechanism given below.



m/z 193
($C_9H_{13}N_4O$)

m/z 175

The fragment ion peak at m/z 175 is fairly strong and is common with other 3β-substituted tetrazoles both in the stig-mastane and cholestane series. This significant peak is useful in identification and characterization of 7a-aza-tetrazoles. The most obvious source for this ion seems to be the ion m/z 193, which on loss of water would give m/z 175.

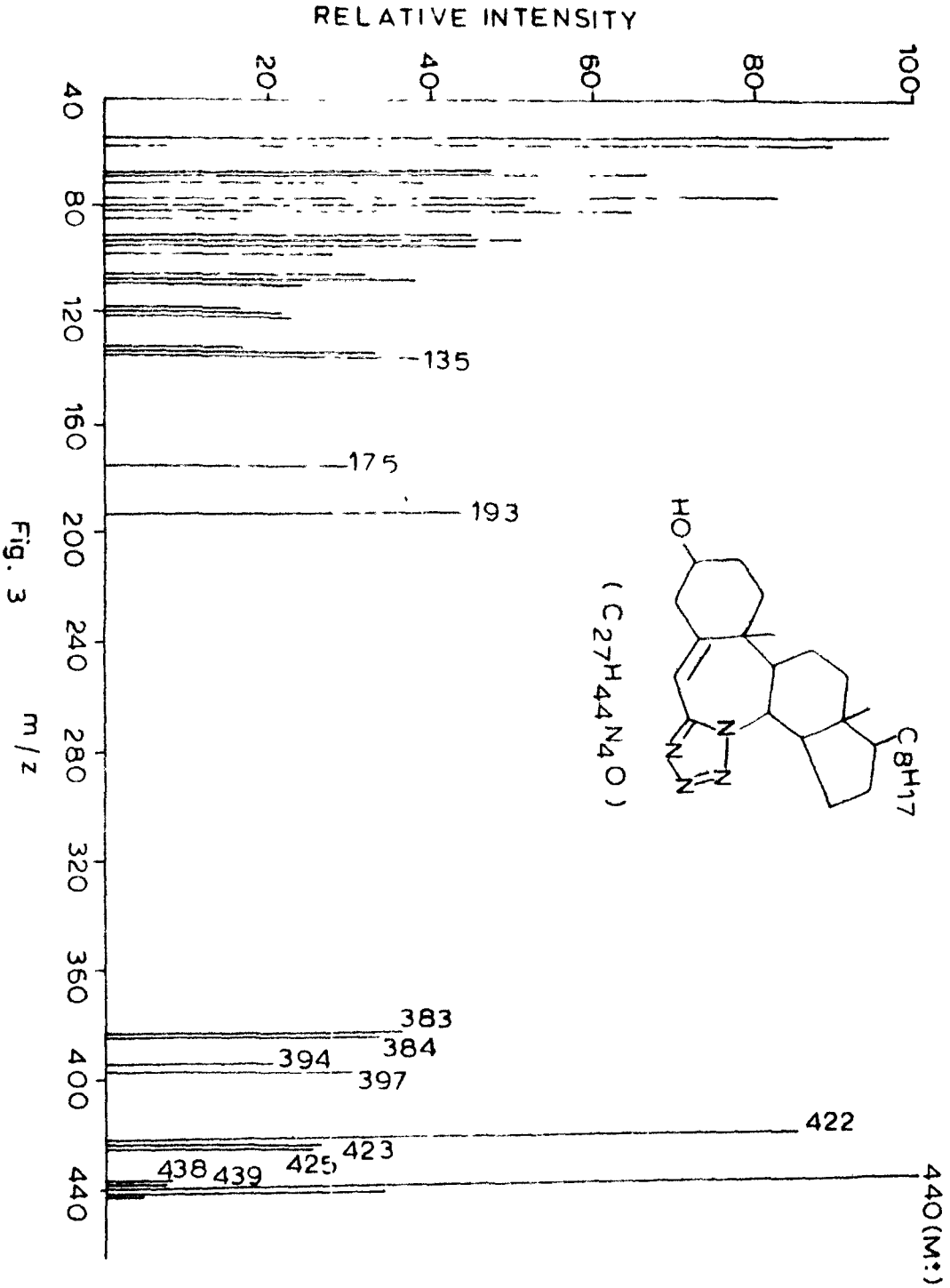


m/z 193 m/z 175 ($C_9H_{11}N_4$)

The mass spectrum of 3β-hydroxy analogue (CLXXXI) (Fig. 3), in the cholestane series gave molecular ion peak at m/z 440 (base peak; $C_{27}H_{44}N_4O$) followed by other important fragment ions at m/z 438, 436, 423, 422, 397, 394, 384, 383, 193, 175, 135 and lower mass peaks. The fragmentation pattern proposed[41] for the formation of these ions are well supported by the similar fragmentation observed in the case of (CCCXXI).

The mass spectrum of 3β-acetoxy-7a-aza-B-homostigmast-5-ene [7a,7-d] tetrazole (CCCXIX) (Fig. 4) gave molecular ion peak at m/z 510 ($C_{31}H_{50}N_4O_2$). Other significant peaks were observed at m/z 495 (M-CH_3), 467 (M-CH_3-N_2), 450 (M-CH_3COOH; base peak), 432, 175, 159, 147, 135 and lower mass peaks. The mass spectrum of (CCCXIX), contrary to the 3β-hydroxy tetrazole (CCCXXI) showed no fragmentation between the ions m/z 432 and m/z 175.

The high mass fragment ions are comparable with those obtained in the case of (CCCXXI) and to that extent the two spectra are expectedly similar.


RELATIVE INTENSITY
20
40
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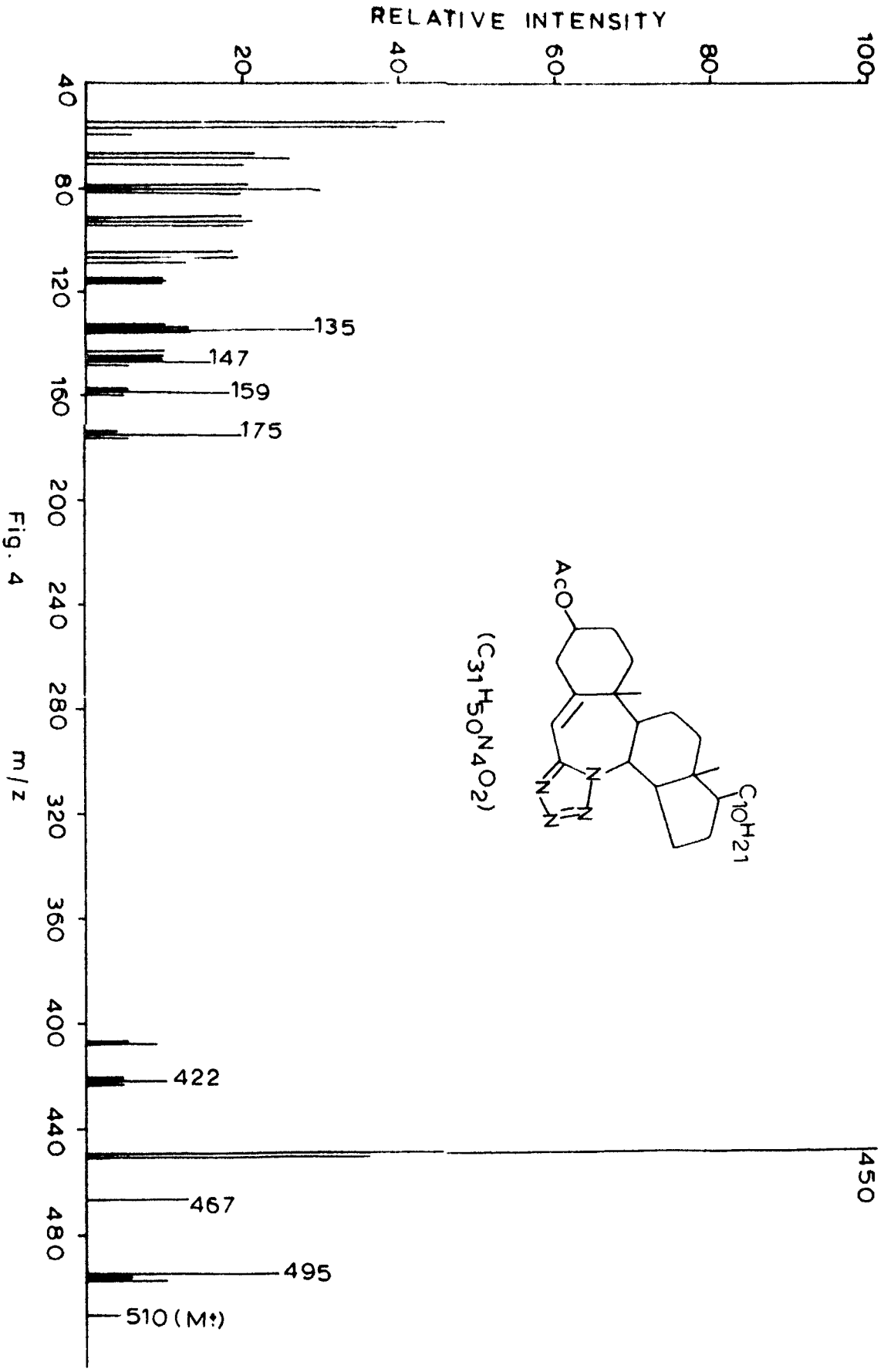
100
40
80
120
160
200
240
280
320
360
400
440
m/z
135
175
193
383
384
394
397
422
423
425
438
439
440(M+)
HO
C8H17
(C27H44N4O)

Fig. 3


RELATIVE INTENSITY
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120
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147
159
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175
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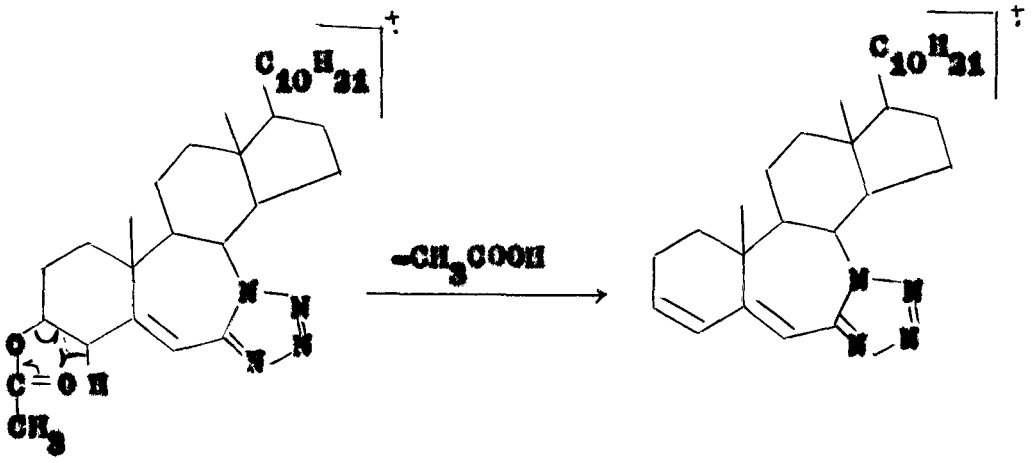
240
280
320
360
400
422
440
450
467
480
495
510 (M+)
m/z
AcO
$C_{10}H_{21}$
$(C_{31}H_{50}N_4O_2)$

Fig. 4

In this case, the molecular ion peak is highly insignificant but M-CH_3COOH is the base peak whereas in case of the hydroxy tetrazole (CCCXXI), the molecular ion peak constitutes the base peak. This observation may be taken as an evidence to show that the loss of acetic acid is a much more ready process than the loss of water from such structurally related compounds.

m/z 450

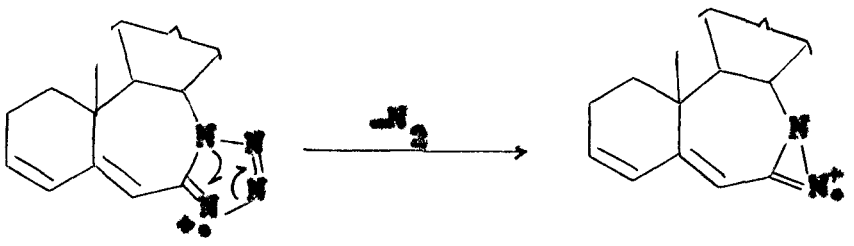
The loss of acetic acid from acetates is well documented[138] and occurs in 1,2-elimination process. Out of the two possible alternatives for the loss of CH_3COOH (C_3-CH_3COO + C_2-H/C_3-CH_3COO + C_4-H), it is possible that the loss may involve predominantly CH_3COO + C_4-H, thus giving rise to a more stable conjugated diene system.



(CCCXIX') m/z 450

m/e 422

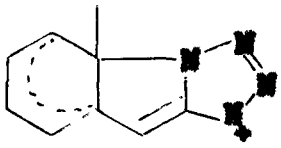
This fragment ion may result by the loss of N_2 from the ion m/e 450 as given below.



m/e 450 m/e 422

m/e 175

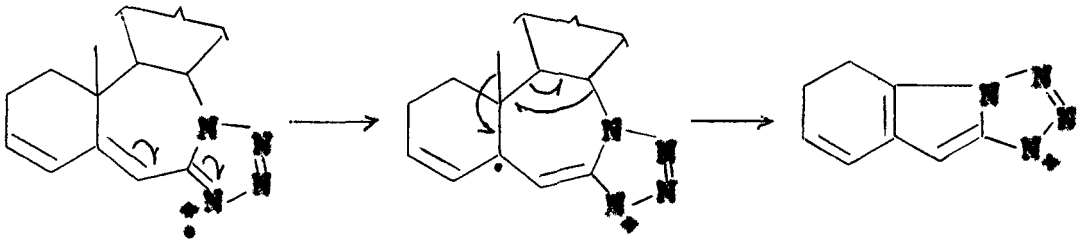
The spectrum is devoid of any mid-range fragmentation between m/e 422 and m/e 175. This observation may be considered as a marked departure from its 3β-hydroxy analogue (CCCXXI). The common fragment ion m/e 175 may be written in the present case as below.



m/e 175

m/z 159

The fragment ion m/z 159 may arise from the ion m/z 450 through a series of concerted elimination reactions.



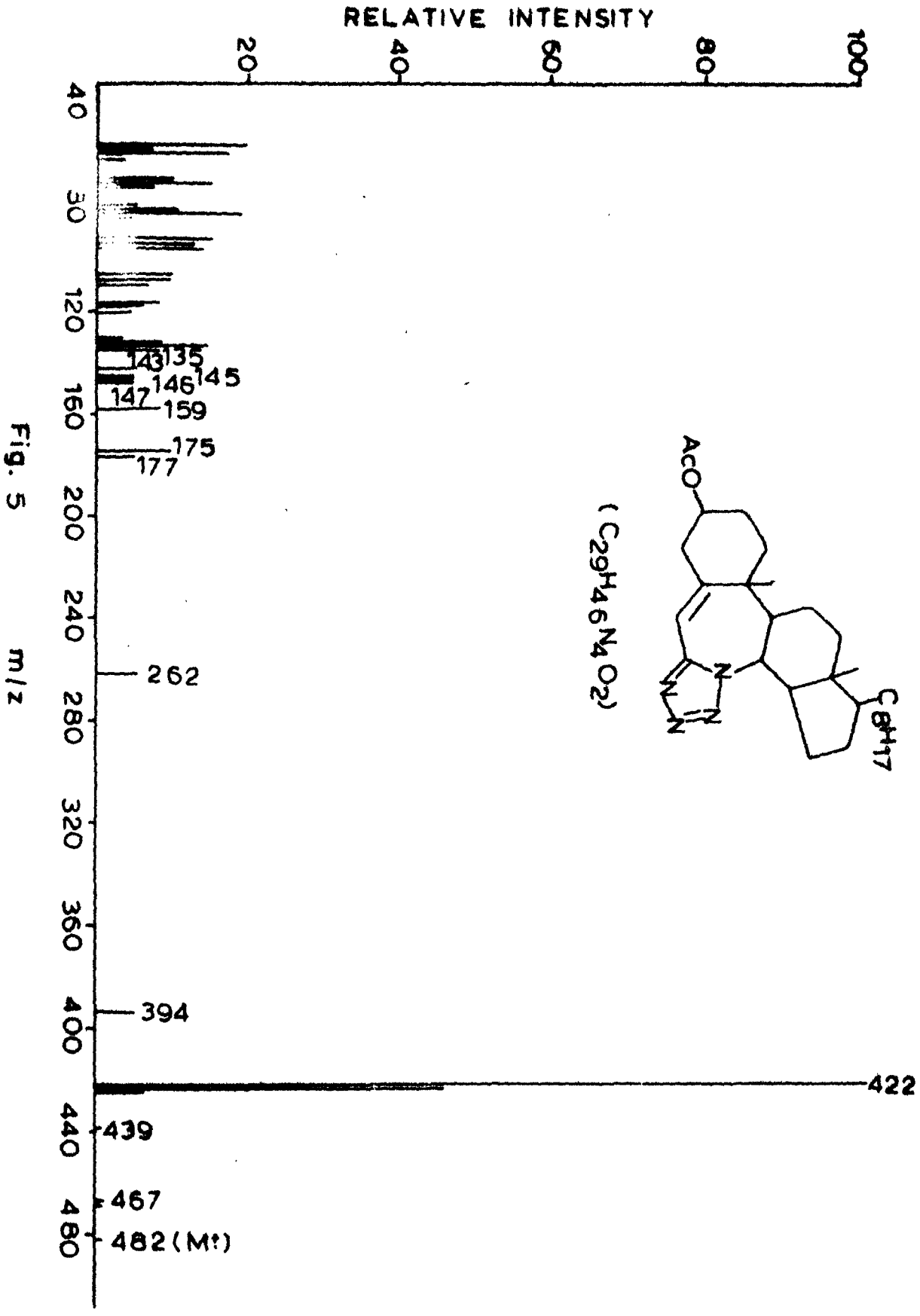
m/z 450 m/z 159

m/z 147

This fragment ion may be suggested to arise by the loss of N_2 from the ion m/z 175.

m/z 175 m/z 147

The comparison of this spectrum with its analogous tetrazole (CLXXX) (Fig. 5) in the cholestane series revealed striking similarity in the fragmentation pathways. It is noted


RELATIVE INTENSITY
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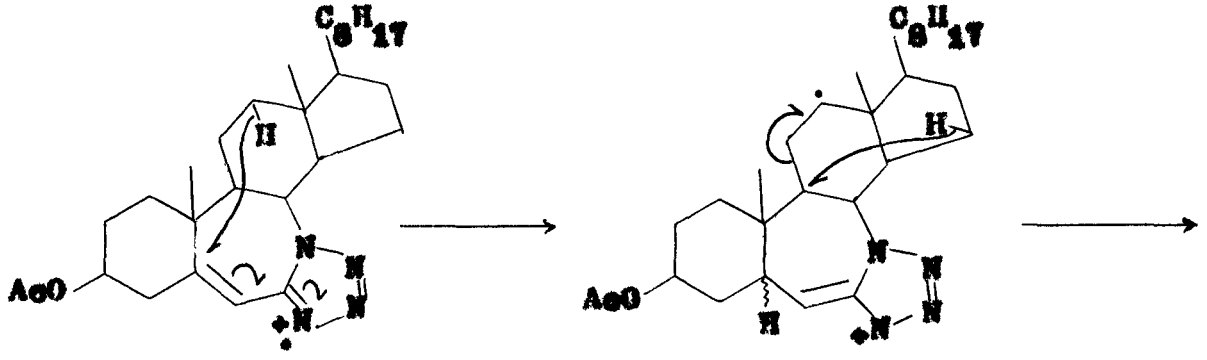
240
262
280
320
360
400
394
422
440
439
467
480
482 (M+)
m/z
AcO
C8H17
(C29H46N4O2)

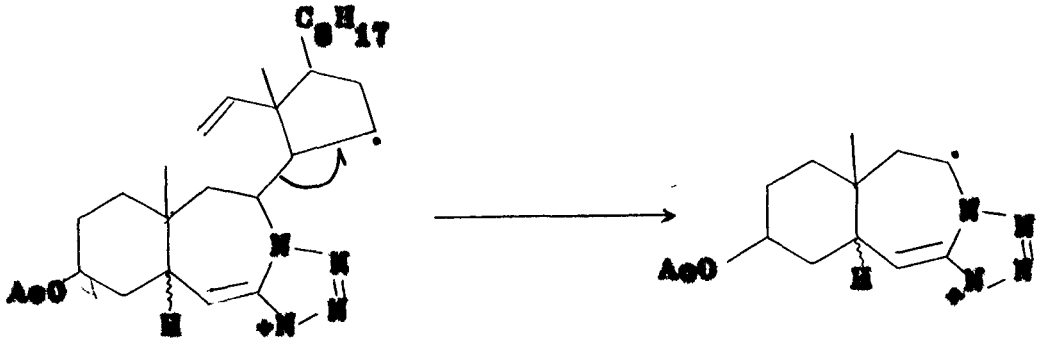
Fig. 5

that in the spectrum of (CLXXX), a fragment ion m/e 262 was observed while it is not found in the case of (CCCXIX). Other high mass fragment ions in (CLXXX) corresponded to those obtained in (CCCXIX) such as m/e 467/495, 439/467, 432/450, 394/422, 175 and lower mass peaks.

The formation of the fragment ion m/e 262, in the case of (CLXXX) only, can be explained in the following mechanism.



(CLXXX')



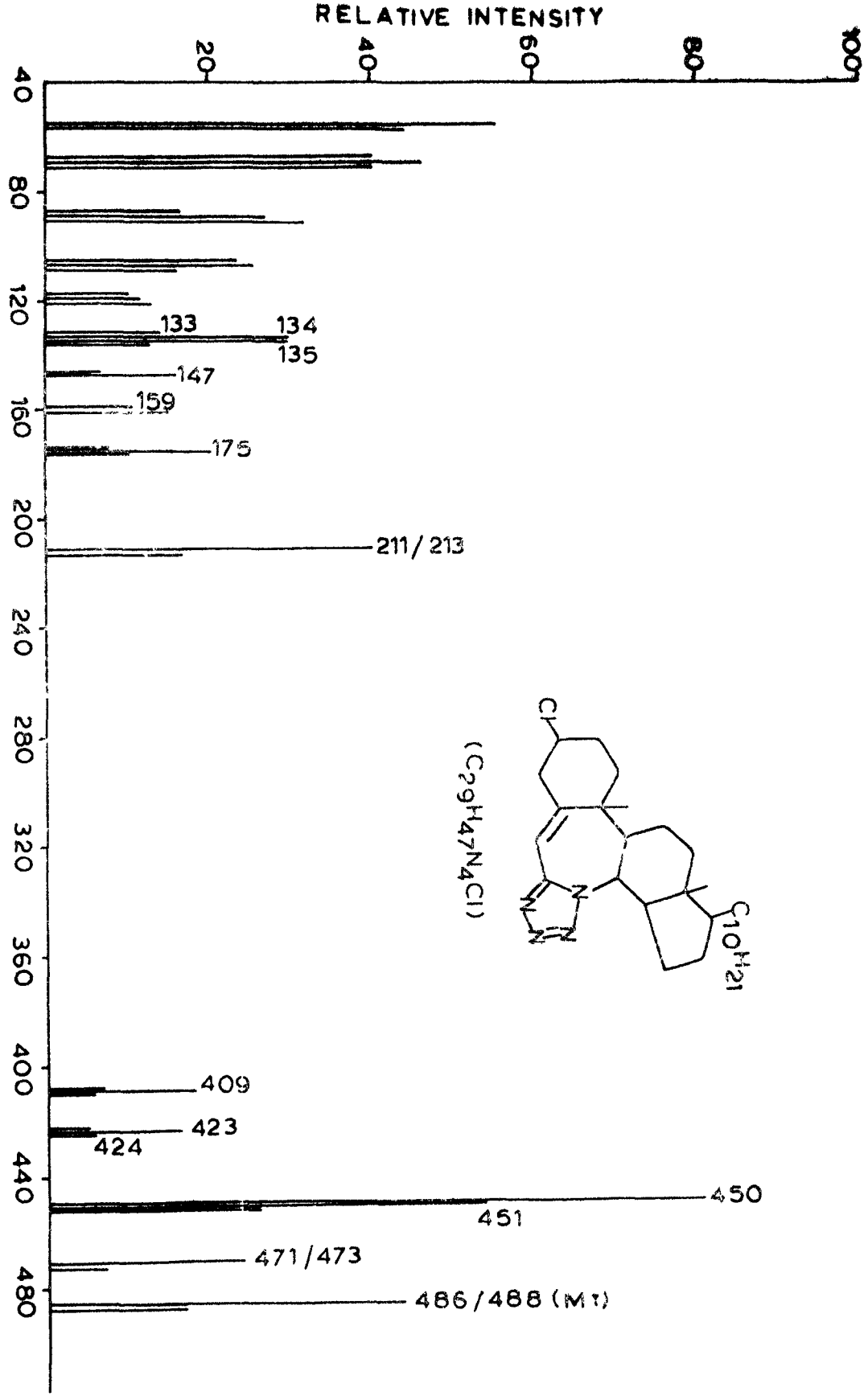
m/e 262

The comparable fragmentation m/e 362 is missing in the spectra of other analogues and it seems to be a hydrocarbon triggered ion. The composition ($C_{13}H_{18}N_4O_2$) compatible with mass unit 362 has been shown to arise by the loss of rings C, D and the side-chain with 1 hydrogen migration to the ring B as shown in the above mechanism.

In this way, the expected behaviour of fragmentation in the stigmastane series, fairly supports the similar findings in the analogous tetrazole (CLXXX), the previously studied 7a-azatetrazole in the cholestane series.

The mass spectrum of 3β-chloro-7a-aza-B-homostigmast-5-ene [7a,7-d] tetrazole (CCCXX) (Fig. 6) is apparently more interesting than the previous two tetrazoles (CCCXXI) and (CCCXIX). It gave molecular ion peak at m/e 486/488 ($C_{29}H_{47}Cl\ N_4$) along with important ion peaks at m/e 471/473 (M-CH_3), 451 (M-Cl), 450 (M-HCl; base peak), 434, 433, 409, 175, 149, 148, 147, 135 and lower mass peaks.

Most of the ions were expected ones and no attempt will be made to write their mode of formation. The fragment ion m/e 450 which constitutes the base peak can be shown to arise by the loss of HCl from the molecular ion as shown below.


RELATIVE INTENSITY
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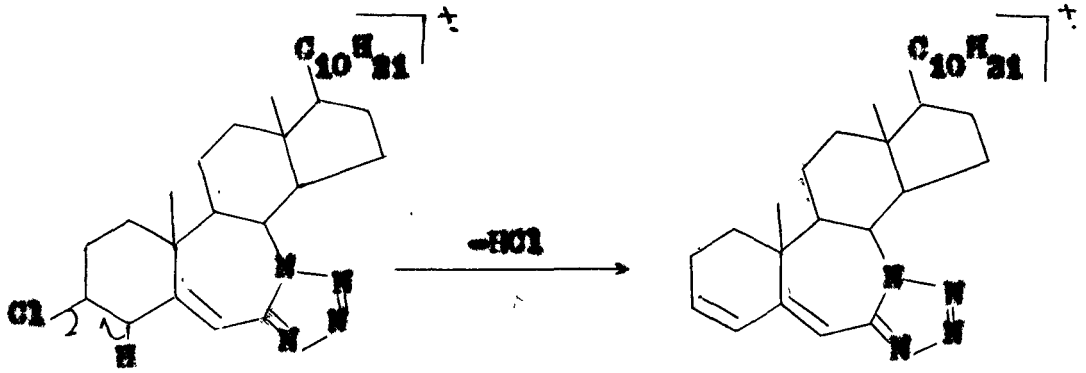
80
120
160
200
240
280
320
360
400
440
480
m/z
133
134
135
147
159
175
211/213
409
423
424
450
451
471/473
486/488 (M+)
Cl
(C29H47N4Cl)
C10H21

Fig. 6



(CCCXX') m/z 450

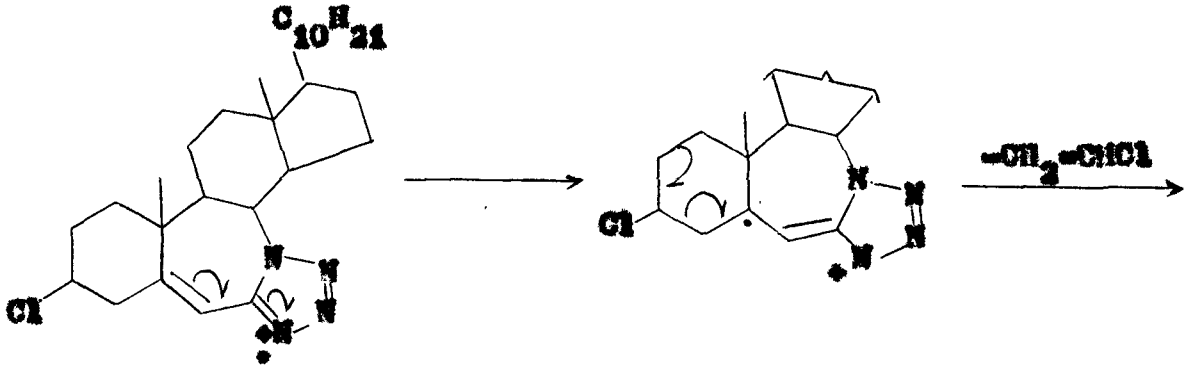
It is worth mentioning here that contrary to this observation, the M-HCl fragment ion (as m/z 423) in the spectrum of 3β-chloro analogue (CXLI) in the cholestane series was not as much significant. It further supports that the loss of HCl is as pronounced as that of acetic acid from acetates.

The other notable features of this spectrum is the presence of distinct ions such as m/z 434 and m/z 409, both chlorine free fragments. They require some additional comments regarding their mode of formation as these ions were not observed in the spectra of (CCCXXI) and (CCCXIX).

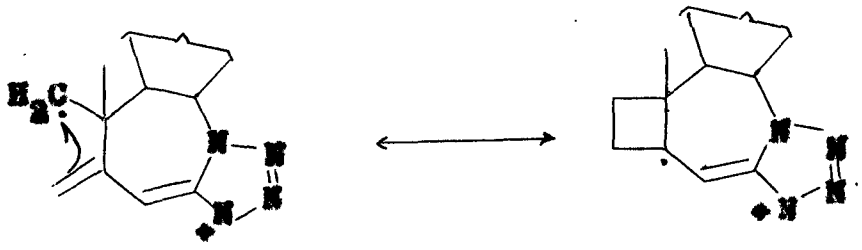
<u>m/z 434</u>

This important fragment ion represents the loss of mass unit 62 (including chlorine) from the molecular ion. The composition of the mass unit 62 could well be as CH_2=CHCl.

Removal of this unit from the molecular ion can be suggested according to the following mechanism.

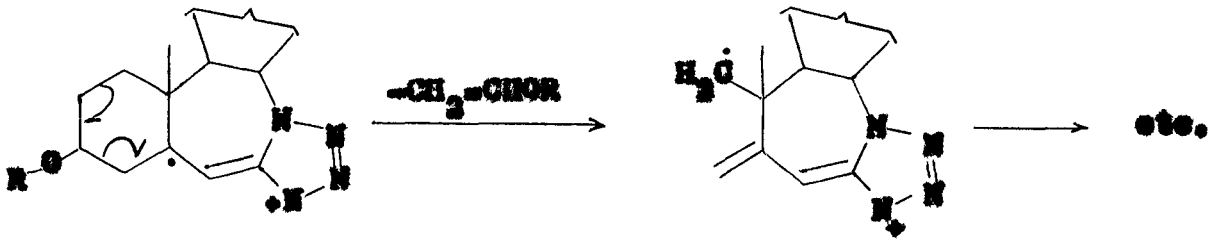


(CCCXX')



m/z 424

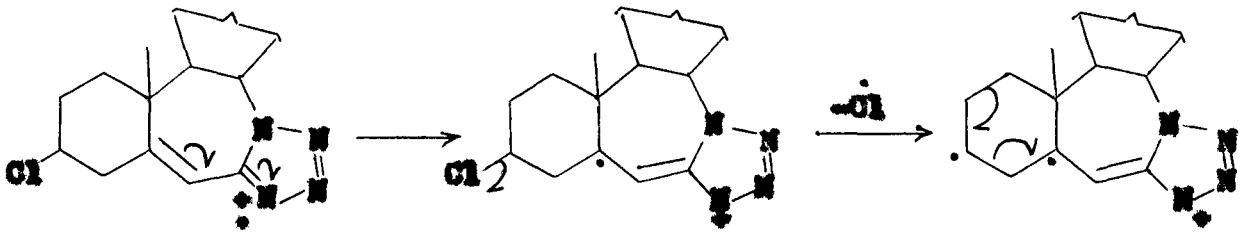
However, according to this approach, a similar mechanism could have operated in the case of (CCCXXI) and (CCCXIX) giving rise to the fragment ion m/z 424 as shown in the following manner.



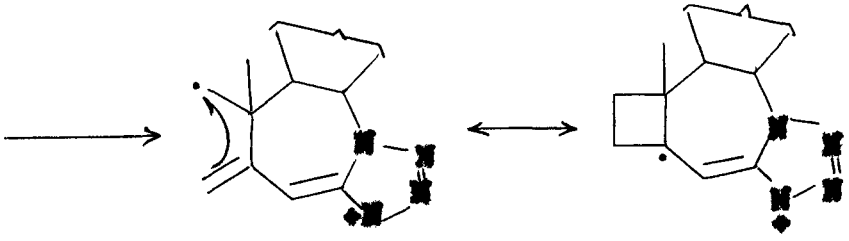
(CCCXXI') R, H
(CCCXIX) R, OAc

m/z 424

Thus in the light of above considerations, the absence of the ion m/z 424 in the spectra of (CCCXXI) and (CCCXIX), it is doubtful that this mechanism is of significance. It is possible that the formation of the ion m/z 424 and for that matter m/z 409, depends upon the fact that chlorine can be ejected as chlorine atom (Cl·), whereas the removal of hydroxyl radical (OH) is generally not recommended (except in small number of cases such as oximes).[128] Taking this into consideration, an alternative mechanism can be proposed for the genesis of the ion m/z 424.



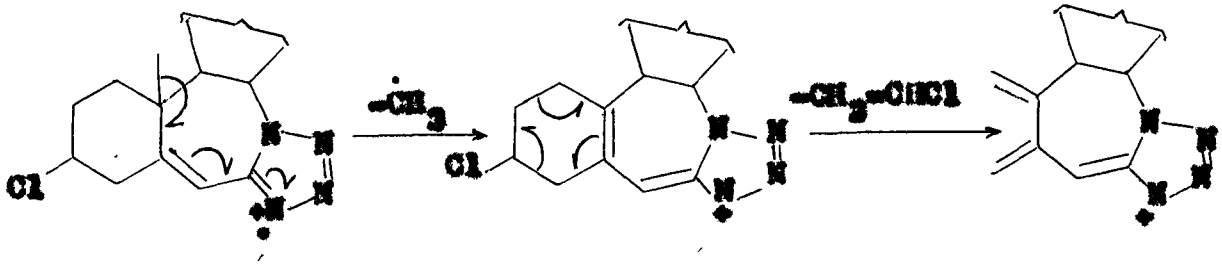
(CCCXX')



m/z 424

m/z 409

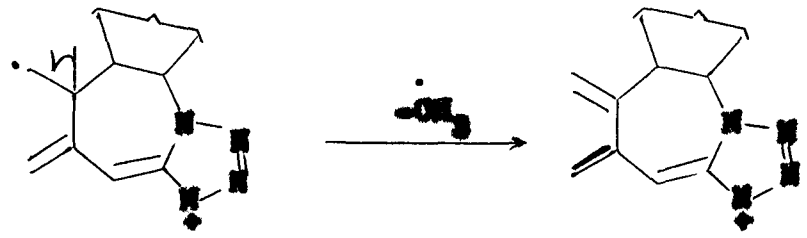
An attractive mechanism for the formation of the ion m/z 409 involving retro-Diels-Alder reaction can be proposed as in the scheme below.



(CCCXX') m/z 409

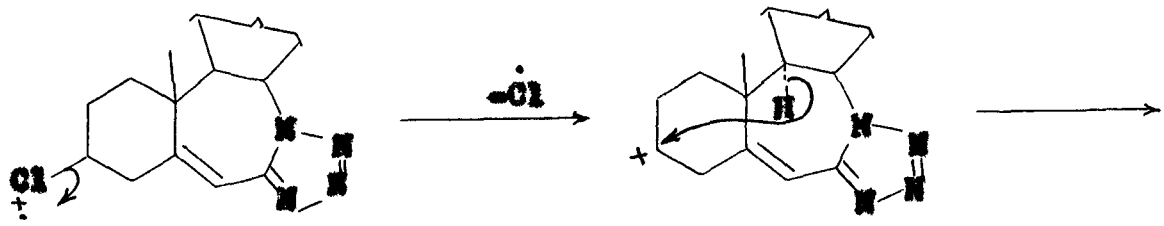
However, the mechanism, if operative seems to be restricted to the chloro tetracles (CCCXX) and (CXLI) only. For some reason, the hydroxy (CCCXXI) and acetoxy (CCCXIX) analogues fail to produce the ion m/z 409 and for that matter in the cholestane series as well.

Alternatively, this fragment ion can be shown to arise from the ion m/z 424 by the loss of a methyl group.

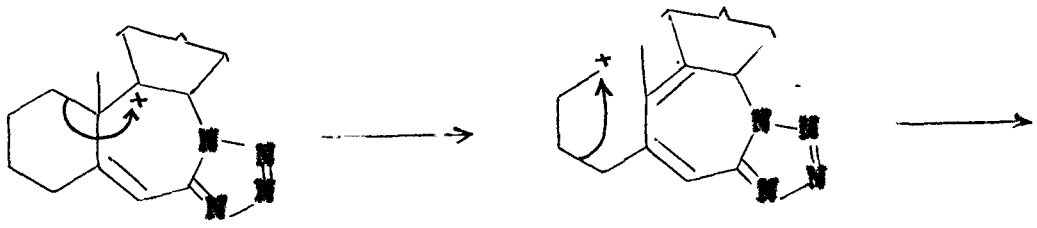


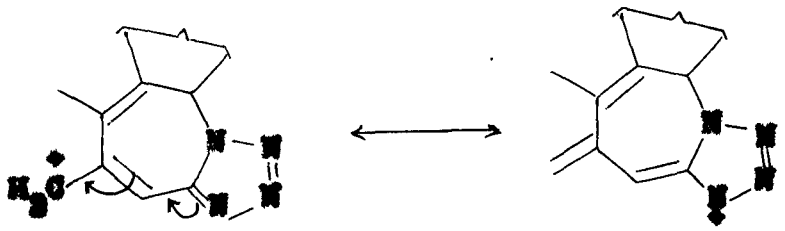
m/z 424 m/z 409

The ion m/e 409 may also be obtained as shown in the following alternative mechanism.



(CCCXX')





m/e 409

The lower mass peaks are comparable with those obtained in the case of (CCCXXI) and (CCCXIX). The only mark of difference noted here is that the fragment ion m/e 301 obtained

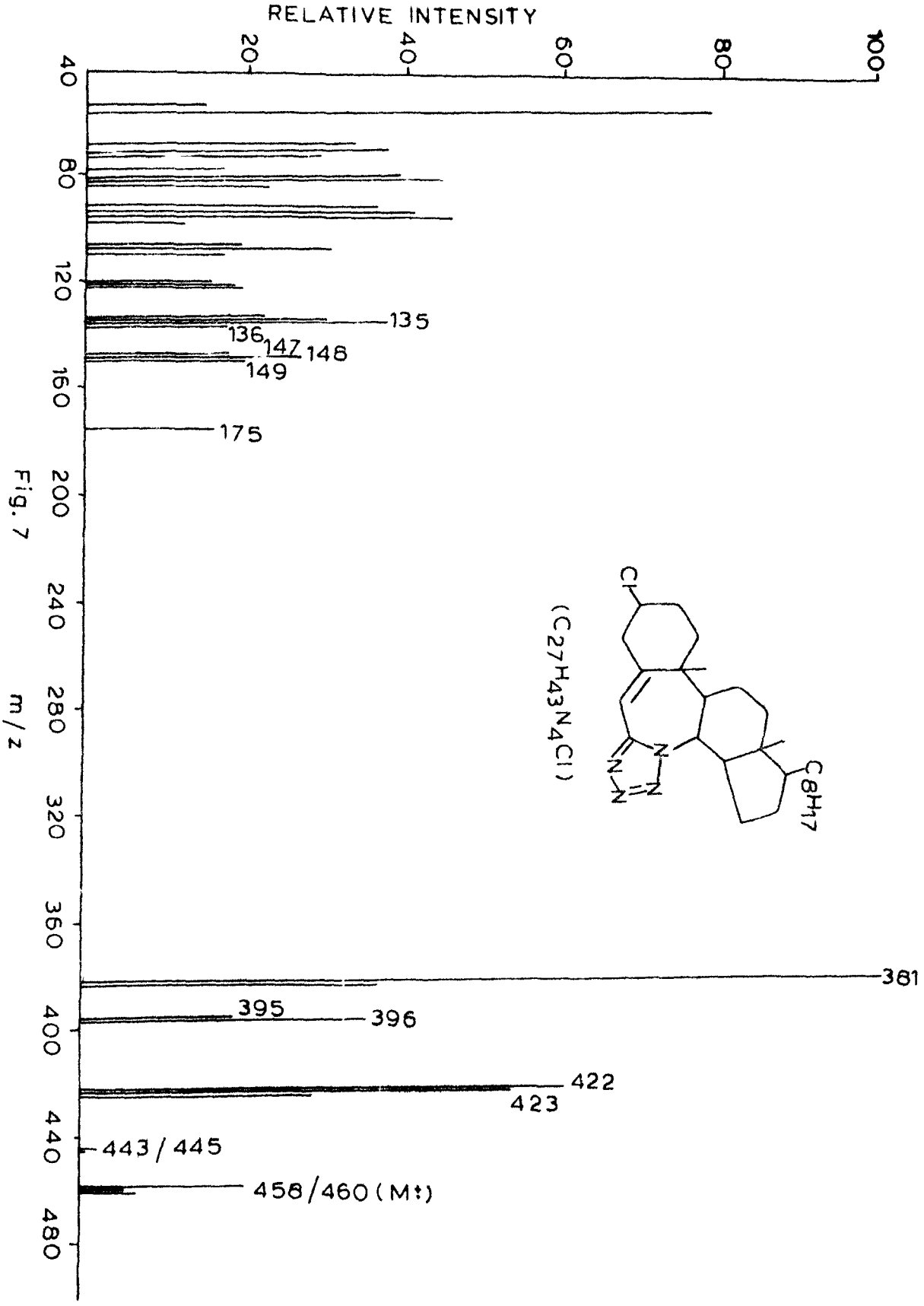

RELATIVE INTENSITY
20
40
60
80
100
40
80
120
160
200
240
280
320
360
400
440
480
m/z
135
136
147
148
149
175
381
395
396
422
423
443 / 445
458/460 (M+)
(C27H43N4Cl)
Cl
C8H17
N
N
N
N

Fig. 7

in the spectrum of 3β-chloro-7a-aza-B-homocholest-5-eno [7a,7-d] tetrazole (CXLI) (Fig. 7) constituted the base peak of the spectrum while its corresponding peak at m/e 409 in (CCCXX) is significantly small and the M-HCl ion (m/e 450) represents the base peak. The other observations are identical and support the fragmentation pathway to a considerable extent.

EXPERIMENTAL

P A R T - I

All melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer 237 spectrophotometer. N.m.r. spectra were run in $CDCl_3$ on a Varian A60 instrument with TMS as the internal standard. U.v. spectra were determined in ethanol with a Beckmann DK2 spectrophotometer. Mass spectra were measured on AEI MS-9 and JMS D-300 mass spectrometers at 70 eV using the direct insertion technique at a source temperature of 250°C. Thin layer chromatographic plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. N.m.r. values are given in ppm (s, singlet; d, doublet; t, triplet; br, broad; mc, multiplet centred at; unc, unresolved multiplet centred at; dd, doublet of doublet). I.r. values are given in cm^{-1} (s, strong; m, medium; w, weak; br, broad).

3β-Acetoxystigmast-5-ene

A mixture of β-sitosterol (100 g), pyridine (150 ml) and acetic anhydride (100 ml) was heated on a water bath for 1-2 hours. The reaction mixture was poured into ice-cooled water, and the solid thus obtained was filtered under suction, washed with water and air-dried. Recrystallisation of the crude product from acetone gave 3β-acetoxystigmast-5-ene (92 g), m.p. 129°.

3β-Acetoxy-6-nitrostigmast-5-ene

To a cooled mixture of 3β-acetoxystigmast-5-ene (10 g) and nitric acid (250 ml; d 1.42) was added sodium nitrite (10 g)

with constant stirring over a period of about 45 minutes. After complete addition of sodium nitrite, stirring was continued for additional 2 hours. Cold water (about 350 ml) was added to the reaction mixture when a solid material was separated. It was extracted with ether and the ethereal layer was washed with water, sodium bicarbonate solution (10%) (until the washing become pink) and finally with water and dried (anhydrous sodium sulphate). Removal of the solvent provided an oil which was crystallised from ethanol to give 3β-acetoxy-6-nitrostigmast-5-ene (4.8 g), m.p. 79°.

Analysis. Found: C, 74.03; H, 10.03; N, 2.76.
Calcd. for $C_{31}H_{51}O_4N$: C, 74.25; H, 10.17; N, 2.79%.

3β-Acetoxy-7-ketostigmastan-6-one (XLII)

3β-Acetoxy-6-nitrostigmast-5-ene (12 g) was dissolved in glacial acetic acid (500 ml) and zinc powder (24 g) added in small portions with shaking. The suspension was heated under reflux for 4 hours and water (25 ml) was added during the course of reaction. The hot solution was filtered, cooled to room temperature and diluted with large excess of water. The precipitate thus obtained was extracted with ether. The ethereal solution was washed with water, $NaHCO_3$ solution (10%), water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent gave an oil which was crystallised

from ethanol to provide the desired ketone (XLII), (8.0 g), m.p. 130-131°. ν max. (Nujol) 1740s ($CH_3\underline{CO}O$), 1710 ($\underline{CO}$) and 1240 cm^{-1} (acetate).

Analysis. Found: C, 78.60; H, 10.8.
Calcd. for $C_{31}H_{52}O_3$: C, 78.81; H, 11.01%.

3β-Acetoxy-3α-bromoetiallocholan-6-one (CCLXXVIII)

3β-Acetoxy-3α-etiallocholan-6-one (XLII) (4 g) in ether (40 ml) and acetic acid (20 ml) was treated with a solution of bromine in acetic acid (40 ml, 5%), the addition was completed over a period of 1 hour (the reaction was catalysed with a few drops of hydrobromic acid). Decolourization proceeded rapidly and a crystalline material started separating after the addition of approximately half of the bromine solution. The reaction mixture was further allowed to stand at 0° for half an hour to ensure complete crystallization. The solid was filtered under suction and recrystallised from light petroleum to yield the desired ketone (CCLXXXVIII), (3.1 g), m.p. 300-301°. ν max. 1705s ($\underline{CO}$), 1735s ($CH_3\underline{CO}$-O), 1235, 1030 (acetate) and 730 cm^{-1} ($\underline{C}$-Br).

Analysis. Found: C, 67.49; H, 9.20; O, 8.68.
Calcd. for $C_{31}H_{51}O_3Br$: C, 67.51; H, 9.25; O, 8.71%.

Baeyer-Villiger oxidation of 3β-acetoxy-5α-bromoetiallocholan-6-one (CCLXXXVIII); 3β-hydroxy-5α-bromoetiallocholan-6-one (CCXC) and 6-oxa-3-homo-5α-bromoetiallocholane-3,7-dione (CCXCI)

3β-Acetoxy-5α-bromoetiallocholan-6-one (CCLXXXVIII)(3 g) was treated with perbenzoic acid (2 mole equivalent) and a few crystals of p-toluenesulphonic acid monohydrate (as catalyst) at room temperature for 50 hours. (The progress of the reaction mixture was checked by t.l.c. after regular interval of time). After completion, the reaction mixture was poured into cold water, extracted with ether, washed successively with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided an oil which was chromatographed over silica gel (40 g). Elution with light petroleum-ether (14:1) furnished (CCXC), recrystallised from methanol, (200 mg), m.p. 140°. νmax. 3330 br (OH), 1700s (C=O) and 720 cm^{-1} (C-Br); δ 3.2 br (1H, C3-$\underline{H}$, axial), 2.3 br,s (2H, C7-$\underline{H}_2$), 0.6s (C_{10}-CH_3), 0.91, 0.8 and 0.72 (other methyl protons).

Analysis. Found: C, 68.31; H, 9.00.
Calcd. for $C_{29}H_{49}O_2Br$: C, 68.36; H, 9.63%.

Further elution with light petroleum-ether (4:1) provided the compound (CCXCI), crystallised from methanol (1.0 g), m.p. 220°. νmax. 1700s (C=O), 1715 (6-lactone carbonyl) and

720 cm^{-1} (C-Br); δ 2.35 br,m (6H, C_3-$\underline{H}_2$, C_4-$\underline{H}_2$, CVe-$\underline{H}_2$), 0.9, 0.81 and 0.78 (methyl protons).

Analysis. Found: C, 66.51; H, 8.91.

Calcd. for $C_{29}H_{47}O_3Br$: C, 66.54; H, 8.98%.

3β-hydroxy-5α-bromoetiocholestan-6-one (CCXC)

A solution of (CCLXXXVIII) (300 mg) in 50 ml of methanolic K_2CO_3 (2%) was heated under reflux for 1 hour. The solution was acidified with HCl and poured into water. The usual work-up provided (CCXC), recrystallised from methanol, (160 mg), m.p. 140°.

3ti,cholest-4-ene-3,6-dione (CCLXXXIX)

β-Sitosterol (10 g) was suspended in acetone (300 ml, distilled over $KMnO_4$) in a three neck round bottomed flask with a stirrer and a dropping funnel. The suspension was stirred for about 30 minutes and then the Jones' reagent ~25 ml was added dropwise from the dropping funnel in course of 45 minutes. The temperature of reaction mixture, during the course of reaction, was maintained to 0-5° by external cooling. After the addition was complete, stirring was continued for additional 30 minutes and then cold water

(200 ml) was added. The product was filtered under suction, washed thoroughly with water and ethanol and air dried. The crude product was chromatographed over silica gel (200 g). Elution with light petroleum-ether (10:1) afforded the desired ketone (CCLXXXIX), crystallised from acetone, (4.5 g), m.p. 156°. ν max. 1680 (C=C-C=O) and 1601 cm^{-1} (C=C); δ 6.08s (1H, C_4-H, vinylic), 3.33m (4H, C_2-H_2, C_7-H_2), 1.16s, 0.9 and 0.73 (other methyls).

Analysis. Found: C, 80.73; H, 10.80; O, 7.50.
Calcd. for $C_{29}H_{46}O_2$: C, 81.69; H, 10.79; O, 7.51%).

Baeyer-Villiger oxidation of stigmast-4-ene-3,6-dione (CCLXXXIX): 5α,7aα-Oxido-6-oxa-B-homostigmastane-3,7-dione (CCXCIII); 3-Oxo-6,7-secostigmast-4-en-6,8-dicarboxylic acid (CCXCIV) and 4α,5α-oxidostigmastane-3,6-dione (CCXCV)

Reaction of stigmast-4-ene-3,6-dione (CCLXXXIX) (2.0 g) with perbenzoic acid (3.5 mole equivalent; 17.95 ml) in the usual manner provided a solid residue which was chromatographed over silica gel (40 g). Elution with petroleum-ether (12:1) yielded the compound (CCXCIII), crystallised from light petroleum, (306 mg), m.p. 105°. νmax. (Nujol) 1792s, 1720s, 1280m, 1140m and 920s cm^{-1}; δ ($CDCl_3$) 5.5s (1H, C_7-H), 2.9d (1H, J 15 Hz; gem coupling), 2.3d (1H, J 15 Hz; gem coupling, C_4-H_2), 1.01, 0.93, 0.86 and 0.70 (other methyls).

Analysis. Found: C, 75.66; H, 9.95; O, 13.78.

Calcd. for $C_{29}H_{46}O_4$: C, 75.98; H, 10.05; O, 13.97%.

Further elution with light petroleum-ether (6:1) gave (CCXCIV), crystallised from light petroleum (180 mg), m.p. 206°. $\nu_{max.}^{(KBr)}$ 3400-3200br (CO-OH), 1720s (C=O) and 1660 cm^{-1} (C=C-C=O); δ ($CDCl_3$) 11.03br,m (2H, $w\frac{1}{2}$ 14 Hz; CO-OH, exchangeable with D_2O), 6.7s (1H, C_4-H), 2.5 (1H, C8-β-H), 2.30br,m (2H, C_2-H_2), 1.3, 1.1, 0.85 and 0.76 (methyl protons).

Analysis. Found: C, 73.28; H, 9.65; O, 16.70.

Calcd. for $C_{29}H_{46}O_5$: C, 73.41; H, 9.70; O, 16.87%.

Further elution with light petroleum-ether (3:1) furnished the noncrystallizable oily compound (CCXCV) (110 mg). $\nu_{max.}^{(KBr)}$ 1720, 1715 (2C=O) and 910 cm^{-1} (>C - C<, with O); δ 3.7s (1H, C4-β-H; $w\frac{1}{2}$ 3 Hz), 1.01, 0.9, 0.85 and 0.70 (methyl protons).

Analysis. Found: C, 78.65; H, 10.31; O, 10.74.

Calcd. for $C_{29}H_{46}O_3$: C, 78.73; H, 10.40; O, 10.85%.

Dimethyl 3-oxo-6,7-secocholestan-4-en-5,6-dicarboxylate (CCCII)

An ethereal solution of the secoacid (CCXCIV) (80 mg) was treated with an excess of an ethereal solution of diazomethane and allowed to stand for 20 minute in the cold. Usual work-up provided (CCCII) as a noncrystallizable oil, (65 mg). νmax. 1725 (CO-OCH_3), 1680 (C=C-C=O), 1190 and 1170 cm^{-1} (methyl

esters); δ 6.4s (1H, C4-$\underline{H}$, vinylic), 3.81s (C_3-OOOC$\underline{H}_3$), 3.68s (C_3-OOOC$\underline{H}_3$), 2.7-3.3 br (C_3-$\underline{H}$ and C_2-$\underline{H}_2$), 1.2, 0.97, 0.78 and 0.65 (methyl protons).

Analysis. Found: C, 73.85; H, 9.90; O, 15.75.

Calcd. for $C_{31}H_{50}O_3$: C, 74.10; H, 9.96; O, 15.93%.

Reaction of (CCLXXXVIII) with an excess of hydrazoic acid: 3β-Acetoxy-5α-bromo-6-aza-5-homocholestane [5,7-d] tetrazole (CCCVIII)

Sodium azide (2 g) was dissolved in water (10 ml) and to this was added benzene (15 ml) at 0°. Sulphuric acid (2 ml) was then added dropwise with shaking over a period of 30 minute at 0-5°; shaking was continued for additional 30 minute and the organic layer was separated, dried over anhydrous sodium sulphate and filtered. This solution of hydrazoic acid in benzene (about 15 ml) was made upto 20 ml by addition of benzene and was treated with freshly distilled boron trifluoride-etherate (1 ml) in the cold. To this was added a solution of the ketone (CCLXXXVIII) (1 g) in benzene (20 ml) in roughly five hour and the reaction mixture kept for 10 days at room temperature. (The progress of the reaction was monitored by t.l.c. to ensure the completion of the reaction). Benzene was removed by distillation under reduced pressure and the residue dissolved in ether. The ethereal solution was

washed with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. After evaporation of the solvent, the crude product was chromatographed over silica gel (20 g) and fractions of 30 ml were collected. Elution with light petroleum-ether (13:1) afforded the tetrazole (CCCVIII), recrystallised from methanol, (360 mg), m.p. 168°. νmax. 1720 ($CH_3-\overset{O}{\overset{\|}{C}}-O-$), 1535, 1450, 1370 (C=N, N=N), 1235, 1030 cm^{-1} (acetate), and 740 cm^{-1} (C-Br); δ 5.25br (1H, C3-α-H, axial, $W\frac{1}{2}$ 16 Hz), 3.5m (2H, C7a-H_2), 2.03s (CH_3-COO), 0.9, 0.86 and 0.68 (methyl groups).

Analysis. Found: C, 65.53; H, 9.01; N, 9.52.
$C_{31}H_{51}N_4Br$ requires : C, 66.54; H, 9.12; N, 10.01%.

Sodium-pentyl alcohol reduction of (CCCVIII)

The 5α-bromotetrazole (CCCVIII) (300 mg) was dissolved in warm amyl alcohol (15 ml) and sodium metal (1 g) was added to the solution with continuous stirring over a period of 8 hour. The reaction mixture was warmed occasionally when all the sodium metal was dissolved, the reaction mixture was poured into 50% HCl (25 ml) and then allowed to stand overnight. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air dried. Crystallisation from methanol afforded the tetrazole (CCCX),

(115 mg), m.p. and m.m.p. 170°. This compound was identical with a sample of the tetrazole (CCCX) obtained from the reaction of the ketone (XLII) with an excess of hydrazoic acid.

Reaction of 3β-acetoxy-5-α-etiallocholan-6-one (XLII) with an excess of hydrazoic acid: 3β-acetoxy-6-aza-B-homo-6-α-etiallocholane [6,7-d] tetrazole (CCCX) and 3β-acetoxy-6-aza-B-homo-6α-etiallocholan-7-one (CCCXI)

The ketone (XLII) (2 g) was treated with hydrazoic acid and boron trifluoride-etherate in the usual manner. The removal of the solvent gave an oil which was chromatographed over silica gel (40 g) and fractions of 25 ml were collected. Elution with benzene-ether (9:1) provided (CCCX), recrystallised from methanol, (1.3 g), m.p. 170°. ν max. 1730 (CH_3-COO), 1530, 1450, 1370 (C=N, N=N), 1260 and 1240 cm^{-1} (acetate); δ4.81 br (1H, C3-α-H, axial, $w\frac{1}{2}$ 14 Hz), 4.26 dd (1H, C5-α-H; J C5-α-H; C_6-β-H 8 Hz; C_5-α-H; C_6-α-H 2 Hz), 3.43 dist.d (C_7-H_2, J 18 Hz), 0.88s (C_{19}-CH_3), 0.91, 0.83 and 0.65 (remaining methyl protons).

Analysis. Found: C, 72.60; H, 9.98; N, 10.06.

$C_{31}H_{52}N_4O_2$ requires : C, 72.65; H, 10.15; N, 10.93%.

Further elution with benzene-ether (4:1) gave (CCCXI), recrystallised from methanol, (400 mg), m.p. 253°. ν max. 3350(NH),

1730 (CH_3-CO-O), 1660 (COCH) and 1240 cm^{-1} (acetate).

Analysis. Found: C, 76.31; H, 10.85; N, 2.86.

$C_{31}H_{53}NO_3$ requires : C, 76.38; H, 10.88; N, 2.87%.

3β-Acetoxyetiocholest-4-en-6-one

A mixture of 3β-acetoxy-5α-bromoetiocholestan-6-one (CCLXXXVIII) (4.0 g) and pyridine (40 ml) was heated under reflux for about 6-8 hour under anhydrous conditions. The reaction mixture was poured into ice-cold water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was crystallized from methanol to give the desired ketone, (3.3 g), m.p. 115°. λ max. 230 mμ; ν max. 1735 (CH_3CO-O), 1680 (C=C-C=O) and 1240 cm^{-1} (acetate); δ6.03d (1H, C4-vinylic proton, J 3 Hz), 2.03s (3H, CH_3-COO), 0.8, 0.75 and 0.68 (other methyl protons).

5α-Etiocholane-3,6-dione (CCLXXXIX)

A mixture of 3β-acetoxyetiocholest-4-en-6-one (4.0 g), concentrated hydrochloric acid (4 ml) and ethanol (100 ml)

was heated under reflux for 2 hour. Half of the alcohol was removed under reduced pressure when the diene (CCLXXXIX) started crystallizing out. The solid was filtered under suction and recrystallised from ethanol, (3.0 g), m.p. 198-199°. $\nu_{max.}$ 1705 and 1710 cm^{-1} (2 C=O).

Reaction of 5α-stigmastane-3,6-diene (CCLXXXIX) with hydrazoic acid: 3,6-Diaza-A,B-bishomo-5α-stigmastane [3,4-d; 6,7-d] bistetrazole (CCCXIV)

A solution of sodium azide (5 g), water (35 ml) and benzene (35 ml) was cooled to 0°. Sulphuric acid (5 ml) was gradually added with shaking over 30 minute and shaking continued for another 30 minute. The organic layer was separated, dried over anhydrous sodium sulphate and filtered. This solution was treated with freshly distilled boron trifluoride-etherate (2 ml) at 0° and a solution of diene (CCLXXXIX)(1.0 g) in benzene (15 ml) added to the cooled hydrazoic acid solution in 5 hour and the reaction mixture left at room temperature for 30 hour. Benzene was removed under reduced pressure, residue extracted with chloroform and washed with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. The crude product obtained on evaporation of solvent was chromatographed over silica gel (30 g). Fractions of 25 ml were collected.

Elution with benzene-ether (9:1) afforded (CCCXIV), recrystallised from light petroleum, (330 mg), m.p. 305°. νmax. 1530, 1470 and 1380 cm^{-1} (C=N, N=N); δ 4.83d (C8-$\alpha\frac{1}{2}$H, J 7 Hz), 4.0m (C8-$\alpha\frac{1}{2}$H, C_2-H$_2$, C_{4a}-H, equatorial), 4.1d (C_{4a}-H, axial, J 10 Hz), 3.25d (1H, C7α-H, J 15 Hz), 1.2s (C_{10}-CH_3), 0.45 (C_{13}-CH_3), 0.86 and 0.78 (other methyl protons).

Analysis. Found: C, 68.35; H, 9.30; N, 21.90.

$C_{39}H_{48}N_8$ requires : C, 68.80; H, 9.44; N, 22.04%.

Chromic acid oxidation of 3β-acetoxyoestr-5-ene: 3β-Acetoxyoestr-5-en-7-one (CCCV)

To a stirred solution of 3β-acetoxyoestr-5-ene (54 g) in glacial acetic acid (600 ml), a solution of chromium trioxide (35 g) in acetic acid (100 ml; 5%) was added over a period of 2 hour, maintaining the temperature around 58-60° throughout. After complete addition, the solution was stirred for an additional period of 2 hour at the same temperature. The excess of chromic acid was destroyed by the addition of methanol (30 ml) and then acetic acid (400 ml) was removed by distillation under reduced pressure. The remaining liquid was diluted with water (25 ml) and allowed to stand in the cold for 12 hour. The crystalline 3β-acetoxyoestr-5-en-7-one (CCCV) which separated as plates, was removed by filtration

under suction and washed with cold acetic acid (30 ml; 80%). Several recrystallisation from light petroleum gave the ketone (CCCV), (8.0 g), m.p. 170°. $\nu_{max.}$ 1725 (CH_3-CO-O), 1670 (C_2C-C=O), 1235 and 1035 cm^{-1} (acetate).

Analysis. Found: C, 79.93; H, 10.42.

Calcd. for $C_{31}H_{50}O_3$: C, 79.14; H, 10.63%.

Reaction of 3β-acetoxyetiallocholest-5-en-7-one (CCCV) with hydrazoic acid: 3β-Acetoxy-7a-aza-B-homoetiallocholest-5-eno [7a,7-d] tetrazole (CCCXIX) and 3β-hydroxy-7a-aza-B-homoetiallocholest-5-eno [7a,7-d] tetrazole (CCCXXI)

The ketone (CCCV)(3 g) was treated with an excess of hydrazoic acid in the usual manner. The crude product obtained on evaporation of the solvent was chromatographed over silica gel (40 g) and eluted in 20 ml fractions. Elution with benzene ether (8:1) gave the tetrazole (CCCXIX), recrystallised from methanol, (1.5 g), m.p. 156°. $\nu_{max.}$ 1735 (CH_3-CO-O), 1660 (C=C), 1510, 1460, 1370 (C=N, N=N) and 1250 cm^{-1} (acetate); δ 6.53s (1H, C_6-vinylic proton), 4.75br (1H, C_3-$\underline{H}$, axial; $w\frac{1}{2}$ 20 Hz), 4.2br (1H, N-C_8-β-$\underline{H}$), 2.05s (3H, CH_3-COO), 1.2s (C_{10}-CH_3), 0.83s (C_{13}-CH_3), 0.87 and 0.75 (other methyl groups). λ max. 240 nm. $M^{+\cdot}$ 510 ($C_{31}H_{50}N_4O_2$).

Analysis. Found: C, 72.90; H, 9.75; N, 11.00.
$C_{31}H_{50}N_4O_2$ requires : C, 72.94; H, 9.80; N, 10.98%.

Further elution with benzene-ether (3:1) afforded the tetrazole (CCCXXI), recrystallised from methanol, (100 mg), m.p. 186°. ν max. 3300br (OH), 1665 (C=C), 1505, 1470 and 1380 cm^{-1} (C=N, N=N); δ 6.58s (1H, C6-$\underline{H}$), 4.25br (1H, C8-$\beta\underline{H}$), 3.75br (1H, C3-$\alpha\underline{H}$, axial; $W\frac{1}{2}$ 24 Hz), 1.33s (C_{10}-CH_3), 0.83s (C_{13}-CH_3), 1.0 and 0.93 (other methyl groups). λ max. 245 nm. M^+ 488 ($C_{29}H_{48}N_4O$).

Analysis. Found: C, 74.31; H, 10.00; N, 12.00.
$C_{29}H_{48}N_4O$ requires : C, 74.35; H, 10.25; N, 11.96%.

Acetylation of (CCCXXI)

A mixture of 3β-acetoxy-7a-aza-B-homocholestan-7-one [7a,7-d] tetrazole (CCCXIX) (80 mg), purified pyridine (0.5 ml) and freshly distilled acetic anhydride (0.4 ml) was allowed to stand at room temperature for 48 hour. The reaction mixture was poured into water and precipitate thus obtained was extracted with ether. The ethereal solution was washed successively with water, dilute hydrochloric acid (until free from pyridine), water, sodium bicarbonate solution (5%) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent provided the crude product (CCCXIX), recrystallised from methanol (50 mg), m.p. and m.m.p. 186°.

3β-Chlorostigmast-5-ene

Freshly purified thionyl chloride (40 ml) was added gradually to β-sitosterol (50 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at a temperature of 50-60° on a water bath for 1 hour, and then poured onto crushed ice with stirring. The yellow solid thus obtained was filtered under suction and washed several times with ice-cooled water and air-dried. Recrystallisation from acetone gave 3β-chlorostigmast-5-ene, (42 g), m.p. 82°.

3β-Chlorostigmast-5-en-7-one (CCCVI)

During 1 hour, a solution of chromium trioxide (26 g) in 80% aqueous acetic acid (36 ml) was added to a vigorously stirred solution of 3β-chlorostigmast-5-ene (50 g) in acetic (600 ml) at 55°. After 2 hour, the excess of chromium trioxide was destroyed by ethanol, the solution concentrated to one third of its volume and water (15 ml) added. The crystalline chloroketone (CCCVI) deposited from the cold solution was recrystallised from light petroleum, (4.5 g), m.p. 156°.

Reaction of 3β-chlorotiganost-5-en-7-one (CCCVI) with hydrazoic acid: 3β-Chloro-7a-aza-B-homostiganst-5-ene [7a,7-d] tetrazole (CCCXX)

To a solution of sodium azide (2 g) in water (10 ml) was added benzene (15 ml) at 0°. Sulphuric acid (2 ml) was then added dropwise with shaking over a period of 30 minutes at 0-5°; shaking was continued for additional 30 minute and the organic layer was separated, dried over anhydrous sodium sulphate and filtered. This solution of hydrazoic acid (about 15 ml) was made upto 25 ml by addition of benzene and then boron trifluoride-etherate (1 ml) was added in the cold. A solution of the ketone (CCCVI) (1 g) in benzene (20 ml) was then added to cold hydrazoic acid solution in roughly 5 hour and the reaction mixture stood for 30 hour at room temperature. (The progress of the reaction mixture was checked by t.l.c. to ensure the completion of the reaction). Benzene was distilled off under reduced pressure and the residue dissolved in ether, washed with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave a semi solid material which was recrystallised from light petroleum-ether to give the chlorotetrazole (CCCXX), (430 mg), m.p. 180°. ν_{max} 1670 (C=C), 1515, 1465, 1380, (C=N, N=N) and 770 cm^{-1} (C-Cl); δ 6.3m (1H, C_8-H, vinylic proton),

4.1br (2H, C_3-αH, axial and C_6-βH; $W_{\frac{1}{2}}$ 20 Hz), 2.7d (2H, C_4-H_2), 1.3s (C_{10}-CH_3), 0.8s (C_{13}-CH_3), 0.85 and 0.9 (other methyl groups). M$^+$ 486/488 ($C_{29}H_{47}N_4Cl$).

Analysis. Found: C, 70.85; H, 9.10; N, 11.35.

$C_{29}H_{47}N_4Cl$ requires : C, 71.43; H, 9.65; N, 11.49%.

Stigmast-5-ene

3β-Chlorostigmast-5-ene (10 g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (30 g) was added to the solution with continuous stirring over a period of 8 hour. The reaction mixture was warmed occasionally. When all the sodium metal was dissolved, the reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand overnight. A white crystalline solid was obtained which was filtered under suction and washed thoroughly with water and air-dried. The crude material was recrystallised from acetone to provide stigmast-5-ene as cubes, (8.3 g), m.p. 75°.

Stigmast-5-en-7-one (CCCIV)

Stigmast-5-ene (6.5 g) was dissolved in glacial acetic acid (35 ml) at a temperature of 75°. A solution of chromium trioxide (8 g) in acetic acid (50%) was added drop by drop

from a dropping funnel with continuous stirring over a period of 2 hour. After complete addition of chromic acid solution, the mixture was stirred for an additional period of 2 hour at 70-75°. The excess of chromic acid was destroyed by addition of methanol (10 ml) and the solvent was removed by distillation under reduced pressure. The residue was extracted with ether (50 ml X 3), the ethereal solution was washed with water and then extracted with four 100 ml portions of sodium hydroxide solution (5%). The ethereal solution left after extraction with sodium hydroxide was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which crystallised from methanol in small plates to give stigmast-5-en-7-one (CCCIV), (740 mg), m.p. 116°.

Reaction of stigmast-5-en-7-one (CCCIV) with hydrazoic acid: 7a-Aza-B-homostigmast-5-ene [7a,7-d] tetrazole (CCCXVIII)

Sodium azide (2 g) was dissolved in water (15 ml) and benzene (15 ml) was added to it. The solution was cooled to 0° and sulphuric acid (2 ml) was slowly added with stirring over 30 minute and shaking continued for an additional 30 minute. The organic layer was separated, dried over anhydrous sodium sulphate and filtered. This solution was diluted to 30 ml by addition of benzene and treated at 0°

with freshly distilled boron trifluoride-etherate (1 ml). A solution of the ketone (CCCIV)(1 g) in benzene (10 ml) was added to the hydrazoic acid solution in 5 hour and the reaction mixture left at room temperature for 30 hour. After completion of the reaction,(checked by t.l.c.), benzene was removed by distillation under reduced pressure and the residue extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. The crude material obtained on evaporation of the solvent was recrystallized from light petroleum-ether which afforded the tetrazole (CCCXVIII), (250 mg), m.p. 140°. ν_{max}. 1665 (C=C), 1510, 1450 and 1380 cm^{-1} (C=N, N=N); δ 6.4s (1H C6-$\underline{H}$, vinylic proton), 4.2br (1H, C8-$\beta\underline{H}$, $W_{\frac{1}{2}}$ 16 Hz), 3.3-3.4m (methylene envelope), 1.2s (C_{10}-CH_3), 0.9 and 0.8 (other methyl groups). M^+ 452 ($C_{29}H_{48}N_4$).

Analysis. Found: C, 75.89; H, 10.10; N, 12.21.
$C_{29}H_{48}N_4$ requires : C, 76.99; H, 10.62; N, 12.39%.

<u>Oxime of stigmast-4-ene-3,6-dione (CCCXXII)</u>

A mixture of the diketone (CCLXXXIX) (2.0 g), hydroxylamine hydrochloride (3.0 g), sodium acetate (4.0 g), water (10 ml) and alcohol (200 ml) was heated under reflux for 2 hour. Most of the solvent was removed by distillation under

reduced pressure, the residue diluted with water and extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent gave the dioxime (CCCXXII), which was recrystallised from light petroleum, (1.6 g), m.p. 195°. max. 3310-3200br (NOH), 1660 cm^{-1} (C=N-OH); 6.0m (1H, C_6-H, vinylic proton), 6.5br (2H, 2N-OH), 3.3m (4H, C_2-H_2 and C_7-H_2), 1.2s (C_{10}-CH_3), 0.75 (C_{13}-CH_3), 0.98 and 0.87 (methyl groups).

Analysis. Found: C, 76.10; H, 10.50; N, 5.94.
Calcd. for $C_{29}H_{48}N_2O_2$: C, 76.31; H, 10.74; N, 6.14%.

Beckmann rearrangement of stigmast-4-ene-3,6-dione oxime (CCCXXII); 6-Aza-B-homostigmast-4-ene-3,7-dione (CCCXXIII) and 3-aza-A-homostigmast-4a-ene-4,6-dione (CCCXXIV)

The dioxime (CCCXXII) (1.0 g) was dissolved in thionyl chloride (10 ml) at -20° and the solution was poured into an excess of 4N potassium hydroxide solution (50 ml) at 20°. The resultant solid material was filtered, dissolved in ether and washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a semisolid material which was chromatographed over silica gel (20 g) and fractions of 30 ml were collected. Elution with

light petroleum-benzene (5:1) gave 3-oxa-A-homoestigmast-4a-ene-4,6-dione (CCCXXIV) which was crystallised from absolute methanol and needle shape fine crystals were obtained, (175 mg), m.p. 210°. ν max. 3250 (CO-NH), 1660 and 1585 cm^{-1} (O=C-C=C-CONH); δ 6.4br (1H, C4a-H, vinylic proton), 6.9br,s (1H, N-H), 2.88m (2H, C_2-H_2), 1.1s (C_{10}-CH_3), 0.7s (C_{13}-CH_3), 0.9 and 0.8 (other methyl groups).

Analysis. Found: C, 78.15; H, 9.95; N, 3.10.

$C_{29}H_{47}NO_2$ requires : C, 78.91; H, 10.65; N, 3.17%.

Further elution with light petroleum-benzene (3:1) afforded 6-oxa-B-homoestigmast-4-ene-3,7-dione (CCCXXIII) which crystallised from methanol, (200 mg), m.p. 152°. ν max. 3260 br (CO-NH), 1665 and 1620 cm^{-1} (O=C-NH-C=C-C=O); δ 6.9br (1H, N-H), 5.9s (1H, C_4-H), 3.2-2.4 br,m (4H, C_2-H_2 and C_7-H_2), 1.2s (C_{10}-CH_3), 0.3s (C_{13}-CH_3), 1.1 and 0.9 (other methyls).

Analysis. Found: C, 78.20; H, 10.10; N, 3.20.

$C_{29}H_{47}NO_2$ requires : C, 78.91; H, 10.65; N, 3.17%.

PART-II

3β-Acetoxycholest-5-ene

A mixture of cholesterol (50 g), pyridine (75 ml) and acetic anhydride (50 ml) was heated on a steam bath for 2 hour. The resulting brown solution was poured onto crushed ice-water mixture with stirring. A light brown solid was obtained, which was filtered under suction, washed with water until free from pyridine and air-dried. The crude product on recrystallization from acetone gave the pure acetate (45 g), m.p. 114-115° (lit.[139] m.p. 116°).

3β-Acetoxy-6-nitrocholest-5-ene

3β-Acetoxycholest-5-ene (5 g) was covered with nitric acid (125 ml; d, 1.53) and sodium nitrite (5 g) was gradually added over a period of 1 hour with continuous stirring. Slight external cooling was also affected during the course of the reaction, and stirring was continued for additional 2 hour when a yellow spongy mass separated on the surface of the mixture. The mixture was diluted with cold water (100 ml) when a green coloured solution was obtained. The whole mass was extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution (10%) (until washings were pink) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided the nitro

compound as an oil crystallised from methanol, (2.5 g), m.p. 104° (lit.[130] m.p. 102-104°).

3β-Acetoxy-5α-cholestan-6-one

3β-Acetoxy-6-nitrocholest-5-ene (2 g) was dissolved in glacial acetic acid (125 ml) by warming the mixture and zinc dust (6 g) was added in small portions with shaking. The suspension was heated under reflux for 4 hour and water (6 ml) was added now and then during the course of the reaction. The hot solution was filtered, cooled to room temperature and diluted with a large excess of ice-cold water. The precipitate thus obtained was taken in ether and the ethereal solution was washed with sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the ketone as an oil which crystallised from methanol, (1.1 g), m.p. 128-129° (lit.[131] m.p. 127-128°).

3β-Acetoxy-5-bromo-5α-cholestan-6-one

To a cooled solution of 3β-acetoxy-5α-cholestan-6-one (2 g) in acetic acid (5 ml) and ether (10 ml), bromine solution (1.1 g of bromine in 15 ml of acetic acid) was added gradually with shaking. Few drops of hydrobromic acid were added to catalyse the reaction. The bromo compound that precipitated out was filtered and recrystallised from chloroform-ether, (1.2 g), m.p. 102-104° (lit.[132] m.p. 102°).

3β-Acetoxycholest-4-en-6-one (LXXXVI)

A solution of 3β-acetoxy-6-bromo-5α-cholestan-6-one (2 g) and pyridine (20 mg) was heated under reflux for 8 hour under anhydrous conditions. The reaction mixture was poured into ice-cold water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was crystallised from methanol to give the ketone (LXXXVI), (1.5 g), m.p. 106-108° (lit.[132] m.p. 110).

Reaction of 3β-Acetoxycholest-4-en-6-one (LXXXVI) with phenylhydrazine : Cholest-3-ene-4-one [4,6-d]-2'-phenylpyrazole (CCCXXX)

A solution of 3β-acetoxycholest-4-en-6-one (LXXXVI) in benzene (25 ml) was treated with phenylhydrazine (1 ml) and acetic acid (3 ml). The reaction mixture was heated under reflux for 4-6 hour. The benzene was removed under reduced pressure and the residue was extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (10%) and finally with water and dried over anhydrous sodium sulphate. Removal of the solvent gave a semi-solid material which was chromatographed over silica gel (20 g) and fractions of 25 ml

were collected. Elution with light petroleum-ether (4:1) furnished cholest-3-ene-4-one[4,6-d]-3'-phenylpyrazole (CCCXXX), recrystallised from chloroform-methanol, (380 mg), m.p. 226°. $\nu_{max.}$ 1650s (C=C-C=O), 1600 (C=C), 1490 (C=N), 750 and 690 cm^{-1}; δ7.8 br.m (NH, aromatic protons), 2.75 m (2H, C_7-H_2), 2.3 m (2H, C_2-H_2), 1.2s (C_{10}-CH_3), 0.66s (C_{13}-CH_3), 1.1, 0.8 and 0.72 (other methyl groups). M^+ 486 ($C_{33}H_{46}N_2O$).

Analysis : Found: C, 81.12; H, 9.30; N, 2.90.
$C_{33}H_{46}N_2O$ requires: C, 81.48; H, 9.46; N, 2.88%.

3β,5,6β-Trihydroxy-5α-cholestane

A mixture of cholesterol (20 g) and formic acid (20 ml; 98%) was heated on a water bath at 70-80° for 5 minute and then allowed to attain room temperature. Hydrogen peroxide (20 ml; 30%) was added to the mixture and it was kept at the room temperature for 12 hour with occasional shaking. Boiling water (Ca 300 ml) was added to the mixture with stirring and the reaction mixture allowed to attain room temperature when a white solid separated which was filtered under suction and air-dried. The solid was dissolved in methanol (600 ml) and the solution heated with sodium hydroxide solution (20 ml; 25%) for 10 minute on a steam bath. It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration under reduced pressure and recrystallised from methanol (16 g), m.p. 237-239° (lit.[128] m.p. 237-239°).

5-Hydroxy-5α-Cholestane-3,6-dione

A suspension of 3β,5, 6β-trihydroxy-5α-cholestane (5 g) in acetone (300 ml) was cooled in an ice-bath. Jones' reagent (15 ml) was added gradually with stirring over a period of 30 minute. Water (200 ml) was added to the reaction mixture and the precipitate thus obtained was collected by filtration under suction. The crude product was subjected to column chromatography over silica gel (100 g). Elution with chloroform gave the dione which was recrystallised from methanol, (3.2 g), m.p. 255° (lit.[134] m.p. 252-253°). $\nu_{max.}$ 3345 m(OH), 1720 s cm^{-1} (C=O).

Cholest-4-ene-3,6-dione (XCII)

A mixture of 5-hydroxy-5α-cholestane-3,6-dione (2 g), dioxan (140 ml) and sulphuric acid (2 ml) was heated under reflux for 1 hour. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with ether. The ethereal solution was successively washed with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Removal of the desiccant and the solvent provided the desired enedione, (XCII), recrystallised from light petroleum, (1.4 g), m.p. 122-123° (lit.[134] m.p. 122-123°).

Reaction of cholest-4-ene-3,6-dione (XCII) with phenylhydrazine: Cholest-3-ene-4-one [4,6-d]-3'-phenylpyrazole (CCCXXX)

A solution of the ketone (XCII) (1.0 g) in benzene (20 ml) was treated with phenylhydrazine (1.0 ml) and acetic acid (2 ml). The reaction mixture was heated under reflux for 8 hour. The benzene was removed under reduced pressure and the residue was extracted with ether. The ethereal layer after washing by usual procedure provided a semi-solid material which was chromatographed over silica gel (20 g). Elution with light petroleum-ether (35:1) provided the compound, (CCCXXX) which was recrystallized from methanol, (320 mg), m.p. and m.m.p. 228°. It was found identical in all respects (t.l.c., co-t.l.c., m.p., m.m.p. and spectral data) with the one obtained from the reaction of 3β-acetoxycholest-4-en-6-one (LXXXVI) with phenylhydrazine.

3β-Hydroxy-5α,6β-dibromocholestane

To a solution of cholesterol (5 g) in ether (30 ml) was added bromine solution (0.9 ml of bromine in 20 ml of glacial acetic acid containing 0.2 g of anhydrous sodium acetate) with stirring. The solution turned yellow and promptly set to a stiff paste of the dibromide. The mixture was cooled in an ice-bath and stirred with a glass rod to ensure complete crystallization. The product was then collected by filtration

under suction and washed with cold acetic acid until the filtrate was completely colourless, (6.9 g), m.p. 112-113° (lit.[135] m.p. 112°).

5α,6β-Dibromocholestan-3-one

The moist dibromide (6.9 g) was suspended in acetone (150 ml) in a three necked round bottom flask fitted with a stirrer and dropping funnel. The suspension was stirred for 5 minute and Jones' reagent[137] (10 ml) was then added in drops from dropping funnel in 15 minute. The temperature of reaction mixture, during oxidation, was maintained between 0-5° by external cooling. After the addition was complete, stirring was continued for 15 minute and cold water (200 ml) was added. The product was collected on a Buchner funnel and washed thoroughly with water and methanol and air-dried, (5 g), m.p. 73-75° (decomposition), (lit.[135] m.p. 73-75°).

6β-Bromocholest-4-en-3-one (LXXVI)

5α,6β-Dibromocholestan-3-one (5 g) was dissolved in absolute methanol (100 ml) by warming on a water bath. Anhydrous potassium acetate (2.5 g) was added to the above solution and the mixture was heated under reflux for 2 hour. The resulting light yellow coloured solution was poured into crushed ice-water mixture and the white precipitate thus obtained

was taken in ether, washed several time with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 6β-bromocholest-4-en-3-one (LXXVI) as an oil which was crystallised from methanol, (3.2 g), m.p. 132° (lit.[137] m.p. 132°).

Reaction of 6β-bromocholest-4-en-3-one (LXXVI) with phenylhydrazine : Cholest-4-eno [4,6-d]-3'-phenylpyrazolo-3-one phenylhydrazone (CCCXXXIII) and cholest-3-one-4-eno [4,6-d]-3'-phenylpyrazole (CCCXXX)

The ketone (LXXVI) (2 g) was dissolved in benzene (30 ml) and to this was added phenylhydrazine (2.5 ml) and acetic acid (3 ml). The reaction mixture was then heated under reflux for 6 hour. Benzene was removed by distillation under reduced pressure. The residue was extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave oily material which was chromatographed over silica gel (50 g) and fractions of 30 ml were collected. Elution with light petroleum-ether (50:1) furnished the compound (CCCXXXIII) which on recrystallisation from methanol afforded fine orange colour crystals, (400 mg), m.p. 195°. $\nu_{max.}$ 3240m (N-H), 1605 (C=C), 1590, 1480 (C-H), 750 and 695 cm^{-1}; δ 7.1-7.5 m(10H, 2-C_6H_5), 12.7 s(1H, N-H), 2.9 m(2H, C_2-H_2), 2.25 d(2H, C_7-H_2; J 10 Hz), 1.2 s(C_{10}-CH_3),

0.73 s(C_{18}-CH_3), 0.9 and 0.8 (other methyls). M^+ 576 ($C_{39}H_{52}N_4$).

Analysis : Found : C, 81.15; H, 9.20; N, 9.40.
$C_{39}H_{52}N_4$ requires : C, 81.25; H, 9.03; N, 9.72%.

Further elution with light petroleum-ether (4:1) afforded the pyrazole (CCCXXX), recrystallised from methanol-chloroform, (300 mg), m.p. and m.m.p. 226°.

Cholest-5-en-3-one

To a solution of 5α,6β-dibromocholestan-3-one (5 g) in ether (100 ml) and acetic acid (2.5 ml) was added zinc dust (7.5)g) in small portions during 30 minute with continuous shaking. After the addition was complete, the ethereal solution containing suspended zinc dust was filtered in separating funnel. The ethereal phase was then washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oily residue which was crystallised from methanol to give the desired ketone, (3.2 g), m.p. 127-128° (lit.[135] m.p. 129°).

Cholest-4-en-3-one (I, [I])

A solution of cholest-5-en-3-one (3.0 g) in ethanol (50 ml) containing oxalic acid (0.6 g) was heated under reflux for 15 minutes. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water,

sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent left an oily residue which was crystallised from ethanol in the cold to give the ketone (LI), (3.8 g), m.p. 80-81° (lit.[135] m.p. 81-82°).

Cholest-4-en-3-one phenylhydrazone (CCCXXXVI)

The ketone (LI) (1.0 g) was dissolved in warm methanol. To this was added a few crystals of p-toluenesulphonic acid (in catalytic amount) and phenylhydrazine (1 ml). The content was heated under reflux for 50 minute. A solid separated after cooling which was filtered on a Buchner funnel. The solid material thus obtained was recrystallised from methanol to give the phenylhydrazone, (CCCXXXVI) (800 mg), m.p. 144°. $\nu_{max.}$ 3330-3420 br(-NH-Ph), 3030, 1600 (aromatic C-H), 1590 and 1495 cm^{-1} (C=N); δ 7.2 br, m (5H, C_6H_5), 6.3 s(1H, C_6-H), 3.3 br, m(2H, C_2-H_2), 1.1 s(C_{10}-CH_3), 0.72 s(C_{13}-CH_3), 0.96, 0.83 and 0.78 (remaining methyls).

Analysis : Found : C, 83.39; H, 10.10; N, 5.48.

$C_{33}H_{50}N_2$ requires : C, 83.89; H, 10.33; N, 5.78%.

Reaction of cholest-4-en-3-one phenylhydrazone (CCCXXXVI) in the presence of acetic acid : 5α-Cholest-3-en-3-one N,N-phenylhydrazone (CCCXXXVII) /3.47

Cholest-4-en-3-one phenylhydrazone (CCCXXXVI) (700 mg) was dissolved in benzene (15 ml) and then was added acetic acid (5 ml). The reaction mixture was heated under reflux for 2 hour. The benzene was removed under reduced pressure and the semi-solid material thus obtained was extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (20 g) and fractions of 25 ml were collected. Elution with light petroleum-ether (22:1) afforded the compound, (CCCXXXVII), recrystallized from methanol, (110 mg), m.p. 135°. $\nu_{max.}$ 3360 br(C-N-H), 1705 s(C=O) 1660, 1530 and 1460 cm^{-1} (C=C-N-N-); δ 9.0 br, s(1H, N-H), 7.4 br, m(5H, C_6H_5), 3.7 s(1H, C_5-αH), 2.67 d(2H, C_7-H_2, J 10Hz), 1.3 s(C_{10}-CH_3), 0.65 s(C_{13}-CH_3), 1.2, 0.9 and 0.8 (remaining methyls). M⁺ 488 ($C_{33}H_{48}N_2O$).

Analysis : Found : C, 80.30; H, 9.20; N, 5.65;
$C_{33}H_{48}N_2O$ requires: C, 81.14; H, 9.83; N, 5.73.

PART - III

The mass spectra were measured on JMS D-300 and AEI MS-9 mass spectrometers at 70 eV using a direct insertion sample inlet system at a source temperature of 250°C. The accurate mass measurements were related to fragment ions of heptacosafluorotributylamine at a resolving power of 15,000.

The value (m/z) of the fragment ions from various steroidal tetrazoles are tabulated below. The values in parentheses are the relative abundance (%) of the peaks with respect to base peak taken as 100% and the compositions of fragment ions as determined by accurate mass measurement.

5α-Androst-2-eno[3α,2-d]tetrazole (CCCXVIII)

M^+ 452 (48.6; $C_{29}H_{48}N_4$), m/z 437 (13.3), 409 (10.0), 177(30.0), 149 (9.3), 135 (15.3), 134 (5.3), 133 (4 .3), 121 (4.6), 119 (6.0), 109 (5.7), 106 (10.0), 104 (10.0), 95 (9.5), 93 (10.0), 90 (9.8), 81 (8.0), 79 (10.0). 69 (7.5). 67 (9.0), 57 (7.5), 55 (8.0), 43 (25.3), 41 (6.8).

3β-Hydroxy-5α-androst-2-eno[3α,2-d]tetrazole (CCCXXI)

M^+ 468 (100.0; $C_{29}H_{48}N_4O$), m/z 466 (16.6), 453 (14.0), 451 (20.0), 450 (93.3), 440 (18.0), 425 (36.0), 422 (25.3), 413 (10.6), 411 (25.3), 408 (18.0), 407 (12.3), 399 (14.6), 397 (20.0), 395 (18.6), 371 (14.6), 194 (13.3), 193 (61.3), 176 (16.0), 175 (80.0), 174 (11.3), 161 (20.0), 159 (54.6), 149 (14.0), 148 (13.6), 147 (22.0), 135 (35.6), 133 (34.0), 132 (14.6), 121 (21.3), 120 (20.0), 119 (22.6), 118 (16.0), 109 (22.0), 108 (38.0), 105 (30.0), 97 (12.6), 95 (39.6),

93 (45.3), 91 (40.0), 85 (16.3), 83 (20.0), 81 (30.6), 79 (39.6), 71 (26.0), 69 (54.0), 67 (34.0), 57 (60.0), 59 (80.0).

3β-Acetoxy-7a-aza-B-homoestigmast-5-ene [7a,7-d] tetrazole (CCCXIX)

M^+ 510 (5.0; $C_{31}H_{50}N_4O_2$), m/e 496 (10.0), 495 (24.0), 467 (19.3), 451 (35.6), 450 (100.0), 423 (4.6), 422 (10.6), 421 (4.6), 421 (4.6), 175 (20.0), 174 (4.0), 160 (4.0), 159 (13.0), 150 (5.3), 149 (5.3), 147 (16.0), 146 (9.3), 145 (10.0), 143 (10.0), 137 (13.3), 135 (30.0), 134 (12.7), 133 (10.0), 117 (10.0), 115 (10.0), 95 (20.6), 93 (21.3), 91 (20.8), 83(20.0), 81 (30.0), 79 (20.8), 71 (20.3), 69 (26.0), 67 (21.3), 60(6.0), 57 (40.0), 55 (46.0).

3β-Chloro-7a-aza-B-homoestigmast-5-ene [7a,7-d] tetrazole (CCCXX)

M^+ 486/488 (44.3:15.0; $C_{29}H_{47}N_4Cl$), m/e 473 (24.0), 471 (6.0), 452 (25.6), 451 (53.3), 450 (80.0), 438 (15.3), 436 (21.3), 434 (5.6), 423 (16.0), 422 (5.6), 410 (6.0), 409 (16.0), 407 (6.6), 213 (16.0), 211 (40.0), 176 (10.0), 175 (20.0), 175 (8.0), 161 (14.6), 159 (10.0), 147 (16.0), 146 (13.3), 136 (12.6), 135 (29.3), 133 (30.0), 131 (14.0), 130 (12.6), 121 (12.8), 119 (11.3), 117 (10.0), 109 (16.0),

107 (25.3), 105 (23.3), 91 (32.0), 89 (26.3), 87 (18.3), 71 (40.0), 69 (46.0), 67 (40.0), 57 (44.6), 55 (55.3),

3β-Hydroxy-7a-oxa-B-homocholest-5-ene [7a,7-d] tetrazole (CLXXXI)

M^+ 441 (30.0; $C_{27}H_{44}N_4O$), m/z 440 (100.0), 439 (6.4), 438 (7.0), 425 (24.9), 423 (26.7), 422 (85.8), 397 (29.4), 394 (20.3), 384 (26.7), 383 (36.2), 193 (44.1), 175 (29.4), 135 (38.5), 133 (33.3), 132 (16.8), 121 (23.3), 119 (21.2), 118 (19.4), 117 (17.6), 109 (24.1), 108 (16.5), 107 (38.5), 105 (32.5), 97 (28.1), 95 (45.7), 94 (21.0), 93 (50.9), 91 (41.1), 85 (17.1), 83 (35.3), 81 (64.9), 79 (51.3), 77 (18.8), 71 (39.2), 70 (21.2), 69 (67.3), 68 (18.6), 67 (47.4), 57 (89.8), 56 (32.5), 55 (96.5).

3β-Acetoxy-7a-oxa-B-homocholest-5-ene [7a,7-d] tetrazole (CLXXX)

M^+ 482 (0.2; $C_{29}H_{46}N_4O_2$), m/z 468 (0.3), 467 (1.3), 439 (0.6), 424 (5.9), 423 (35.2), 422 (100.0), 394 (5.9), 382 (6.3), 177 (5.4), 175 (9.1), 159 (8.7), 147 (7.0), 146 (5.7), 145 (4.8), 143 (6.3), 135 (6.5), 134 (3.7), 133 (14.7), 132 (8.7), 131 (5.1), 121 (4.8), 119 (6.1), 118 (6.4), 117 (6.8), 109 (4.8), 108 (3.7), 107 (10.3), 105 (10.2), 97 (3.8), 97 (3.8), 95 (13.2), 93 (12.7), 95 (13.2), 93 (12.7), 91 (12.7), 83 (4.6), 81 (16.4),

79 (11.0), 77 (5.6), 71.(7.7), 69 (12.7), 67 (10.7), 60 (3.8), 57 (17.9), 56.(7.4), 55 (20.5).

3β-Chloro-7a-aza-B-homocholest-5-ene[7a,7-d] tetrazole (CXLI)

M^+ 458/460 (20.3:7.0; $C_{27}H_{43}ClN_4$), m/z 443/445 (2.3:0.8), 424 (26.7), 423 (56.2), 422 (60.4), 396 (36.2), 395 (18.7), 382 (32.8), 381 (100.0), 175 (16.2), 149 (19.9), 148 (27.4), 147 (18.1), 136 (16.2), 135 (38.2), 134 (29.7), 133 (22.6), 121 (19.4), 120 (18.6), 119 (16.1), 109 (17.8), 108 (15.4), 107 (30.5), 105 (19.6), 97 (14.0), 95 (44.5), 94 (15.6), 93 (39.2), 91 (35.5), 83 (23.6), 81 (46.1), 79 (39.2), 77 (17.8), 71 (30.2), 70 (18.4), 69 (38.2), 67 (33.4), 57 (60.9), 56 (18.7), 55 (79.1), 53 (15.6).

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LIST OF PUBLICATIONS

1. Mass Spectral Studies on Steroidal Compounds-IX: 7a-Acetotrienoles in the Cholestane and Stigmastane Series.
   Org. Mass Spectrom., (Accepted with some modification).

2. Peracid Oxidation of Some 5α-Substituted-6-Ketosteroids.
   Ind. J. Chem., (In press).